Joint ILAE and IFCN minimum standards for recording routine and sleep EEG

Peltola ME1, Leitinger M2, Halford JJ3, Vinayan KP4, Kobayashi K5, Pressler RM6, Mindruta I7, Mayor LC8, Lauronen L1, Beniczky S9

1HUS Diagnostic Center, Clinical Neurophysiology, Clinical Neurosciences, Helsinki University Hospital and University of Helsinki, Helsinki, Finland

2Department of Neurology, Christian Doppler University Hospital, Paracelsus Medical University Salzburg, Austria

3Department of Neurology, Medical University of South Carolina, Charleston, SC, USA

4Department of Pediatric Neurology, Amrita Institute of Medical Sciences, Cochin, Kerala, India

5Department of Child Neurology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

6Clinical Neuroscience, UCL- Great Ormond Street Institute of Child Health and Department of Clinical Neurophysiology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK

7Department of Neurology, University Emergency Hospital of Bucharest and University of Medicine and Pharmacy “Carol Davila”, Bucharest, Romania

8Department of Neurology, Hospital Universitario Fundacion Santa Fe de Bogota, Colombia

9Department of Clinical Neurophysiology, Aarhus University Hospital, Aarhus, and Danish Epilepsy Centre, Dianalund, Denmark

Corresponding author: MD, PhD Maria Peltola, Stenbäckinkatu 9, PL290, 00029 Helsinki, Finland; email: maria.peltola@hus.fi

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Summary
This paper provides recommendations on minimum standards for recording routine ("standard") and sleep EEG. The Working Group of the International League Against Epilepsy (ILAE) and the International Federation of Clinical Neurophysiology (IFCN) developed the standards according to the methodology suggested for epilepsy-related clinical practice guidelines by the Epilepsy Guidelines Working Group. We reviewed the published evidence using the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement. The quality of evidence for sleep induction methods was assessed by the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) method. A quality assessment tool for diagnostic accuracy studies (QUADAS-2) was used to assess risk of bias in technical and methodological studies. When high quality published evidence was lacking, we used modified Delphi technique to reach expert consensus. The GRADE system was used to formulate the recommendations. The quality of evidence was low or moderate. We formulated 16 consensus-based recommendations for minimum standards for recording routine and sleep EEG. The recommendations comprise the following aspects: indications, technical standards, recording duration, sleep induction and provocative methods.

Key points

1. Minimum standards are needed to improve accuracy, efficacy and reliability of recording routine and sleep EEG.
2. These minimum standards were developed by a working group of the ILAE and the IFCN.
3. The overall quality of research evidence was low leading to conditional recommendations.
4. High quality studies assessing methods and diagnostic accuracy of routine and sleep EEG are needed in the future.
1 Introduction

Non-invasive EEG remains an essential method for analyzing electrophysiological brain activity in epilepsy and in selected disorders of brain dysfunction\textsuperscript{1,2}. Although, practical definition of epilepsy is clinical\textsuperscript{3}, scalp EEG has an important role not only in the diagnosis of epilepsy, but also in the follow-up if the disease evolves and the classification of the epilepsy syndromes\textsuperscript{2,4,5}.

The ILAE Neurophysiology Task Force “The role of EEG in the classification of the epilepsy syndromes: a tool for clinical practice” has recently addressed the use of EEG as a clinical tool\textsuperscript{4,5}. Regarding the variable resources of EEG service worldwide, they distinguished two levels of EEG recording, basic and advanced. Routine EEG with activation procedures corresponds to the basic level and sleep induction is used at the advanced recording level. Epileptiform discharges are modulated by sleep and show higher frequency in NREM sleep than awake\textsuperscript{6–8}. Most clinical studies suggest an added diagnostic value of sleep EEG compared to standard EEG\textsuperscript{9–12}, yet a few studies question the utility of sleep EEG\textsuperscript{13,14}. The sensitivity of EEG for epileptiform discharges increases with repeated recordings\textsuperscript{15} and if one repeats the EEG, it is recommended to do a sleep EEG in the second round. In some patients (especially children), the routine wake recording can be so obscured by artefact such that little undisturbed background is visible, in which case a sleep EEG is recommended.

Establishing and maintaining technical standards aim at ensuring the high quality of laboratory investigations. The minimum standards represent a set of standards that can be readily adapted by countries and applied to laboratories at every level of the health-care system\textsuperscript{16}.

The Commission on European Affairs of the ILAE has published in 2002 recommendations for recording EEG across Europe\textsuperscript{17}, but this has not been updated since. A survey organized in 2017 within 28 members the European Reference Network for rare and complex epilepsies (ERN EpiCARE) showed that
almost all centers used local guidelines to record EEG\textsuperscript{18}. In addition, a lack of common standards for recording routine EEG impedes high quality multicenter research projects as was observed in the recently completed Human Epilepsy Project 1 (unpublished data).

American and Canadian Societies of Clinical Neurophysiology and French Society of Clinical Neurophysiology and French League Against Epilepsy have recently published updated national recommendations for EEG recording standards\textsuperscript{19–21}. The lack of international comprehensive guideline for recording EEG impedes the development of global standards for good clinical practices\textsuperscript{22}.

The ILAE and the IFCN identified the need for a new joint recommendation targeting the minimum recording standards of EEG. The ILAE Guidelines Task Force approved the Working Protocol that was based on the methodology recommended by the ILAE for developing a Clinical Practice Guideline\textsuperscript{23}. The protocol followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Appendix 1).

Objective of this joint ILAE-IFCN paper is to provide recommendations on minimum standards for recording routine and sleep EEG. Target audience of the guideline is healthcare personnel referring patients to EEG, being responsible of EEG recordings, analyzing and reporting EEG.

2 Methods
2.1 Establishing a working group
The ILAE and the IFCN each appointed members to the CGP Working Group. The working group composed of ten experts who were adult and pediatric neurologists with subspecialty in epileptology and clinical neurophysiologists. Members represented four of six WHO regions. The working group has been approved by the ILAE Guidelines Task Force.
2.2 Developing clinical questions
To achieve the overall objective, the working group defined five questions that were examined by five subgroups each containing 2-3 working group members (Table 1). PICO statement was used to organize the clinical questions when applicable.

2.3 Search strategy
The literature search was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. We performed electronic search of PubMed and EMBASE databases for English literature between 1990 and September-December 2019. The full search strategies for PubMed and dates when last accessed the database are presented in Appendix 2. Search terms for five clinical questions included:
1. “routine EEG”, “sleep EEG”, “outpatient EEG”, “indication” and “referral”
2. “technical requirements”, “technical standards”, “minimal standards”, “minimum standards”, “standard EEG recording” and “routine EEG recording”
4. “sleep”, “EEG recording”, “diagnosis”, “diagnostic”, “melatonin”, “sleep deprivation” and “induction”

2.4 Study selection, data extraction and synthesis of results
Specific inclusion criteria were defined for each five clinical questions. Studies on neonatal EEG, emergency EEG, intensive care monitoring and long-term epilepsy monitoring were excluded, as they were beyond the scope of this guideline. We included:

1. Studies that addressed the utility of non-emergent EEG in diagnostics or follow up of patients; randomized control trials were searched for, but also studies evaluating the usefulness of EEG if a proper control group (no EEG) and follow up measures (impact on the patient care) were used.
2. Studies that addressed recording electrode array and montages, electrode impedance, synchronized video, sampling rate and frequency band, ancillary equipment, display settings, data storage and EEG data format.

3. Studies that compared yield of different length of EEG recordings and used the presence of EEG abnormalities as a primary outcome measure, and cost-benefit as a secondary outcome.

4. Studies that compared EEG recordings with sleep deprivation (either 24h or partial), studies with no sleep deprivation, studies that compared sleep deprivation to pharmacological sleep induction and studies that compared EEGs with different pharmacological sleep inductions, and studies with yield of sleep as outcome. Secondary outcomes included adverse effects and cost-benefit ratio of sleep induction.

5. Studies that addressed the utility of activations other than sleep and had the yield of epileptiform abnormalities, epileptic seizures, and non-epileptic psychogenic seizures as outcomes. Secondary outcomes included adverse effects.

At least two members of the subgroups independently reviewed the titles and abstracts to identify potentially eligible research articles. References of selected articles were screened for potentially eligible studies. Full text articles were reviewed by two independent reviewers for inclusion. Data extraction was designed independently for each clinical question.

2.5 Quality rating of individual studies and synthesis of results

We used the GRADE method to assess the risk of bias of individual sleep induction studies that were pharmacological and non-pharmacological intervention studies \(^{23,24}\) (Tables S11-S13). In other (non-interventional) studies, risk of bias was assessed by using a quality assessment tool for diagnostic accuracy studies (QUADAS-2) tool developed for primary diagnostic accuracy studies that better targeted potential study limitations involved in technical and methodological EEG studies, although not
being diagnostic accuracy studies\textsuperscript{25} (Tables S9-S10, S14-S15). The risk of bias assessment was carried out by two reviewers that solved possible disagreements by discussion.

In addition, we classified studies as meta-analysis, systematic reviews, randomized controlled trials (RCT), observational studies including diagnostic accuracy studies, case series and guidelines. Observational studies were further categorized, using predefined criteria to evaluate the evidence reflecting risk of bias given the paucity of high-level evidence\textsuperscript{2,26}. Category I observational studies included large (N>50) prospective broad-spectrum studies and large blinded technical studies with an acceptable gold standard. Category II studies were large prospective narrow-spectrum studies, large retrospective broad-spectrum studies and small (N=10 – 50) blinded technical studies with an acceptable gold standard. Category III studies were large retrospective narrow-spectrum studies, small prospective and retrospective studies or technical studies that were not blinded or without an acceptable reference standard. Category IV were mathematical simulation studies.

Due to large heterogeneity of the studies, meta-analysis was not possible to conduct, and our synthesis was qualitative.

2.6 Methods of recommendation
We assessed the overall quality of evidence for methods of sleep induction and yield of sleep during EEG recording using GRADE (Table S13) and for outcomes of other clinical questions by the risk of bias and classification and category of individual studies (Tables S1-S2, S7-S10, S14-S15). Due to low overall quality of evidence, a modified Delphi process was used to formulate recommendations by each subgroup\textsuperscript{27}. The modified Delphi process consisted of a series of written questionnaires that were answered anonymously (Appendix 3), followed by open consensus discussions concerning each clinical question. The iteration was continued until agreement of at least 2/3 of the working group members was achieved. One member of each subgroup designed the Delphi questions, provided supportive analysis of literature, did not answer to written questions but analyzed results and chaired the
consensus discussion that was organized as a web-meeting. The strength of the recommendation was rated following the ILAE guideline of developing clinical practice guidelines.

3 Results

3.1 Indications of routine and sleep EEG
We found 121 articles through database search and six additional articles from other sources. After removing the duplicates, 99 articles remained for screening of abstracts. Fourteen full-text articles were assessed for eligibility. Three guidelines were included. None of the 11 research studies met the eligibility criteria. The reason for exclusion was lack of proper study design and methodology to study the indications for routine and sleep EEG. Screened studies described EEG finding on specific illnesses. PRISMA chart is included in Appendix 4A.

Previous consensus-based guidelines on the best practice of recording and reporting of EEG in adults and children include the general indications for EEG\cite{1,17,21}. They all lay particular emphasis on the clinical suspicion of epilepsy as the main indication of EEG. Recently published clinical summaries determine the value of EEG for the diagnosis of seizures and epilepsy and monitoring of epilepsy\cite{2,4,5,28}. They discuss the sensitivity and specificity of interictal epileptiform discharges, the value of routine and sleep EEG in the diagnosis and classification of the epilepsy type and the role of EEG in making decisions regarding antiseizure medication withdrawal.

3.1.1 Recommendation
We conclude that there is no evidence on indications of routine and sleep EEG. Through a modified Delphi technique, we reached a consensus on the indications of routine and sleep EEG that justifies a weak (conditional) recommendation on the indications of EEG recorded by appointment in non-emergent situation (Table 2).
3.2 Technical standards
Eighteen articles were found in the search and 14 additional articles were identified through other sources. After removal of duplicates, 30 abstracts were screened for eligibility and ten full-text articles were included in the qualitative synthesis. PRISMA chart is included in Appendix 4B. Four of the articles were guidelines\textsuperscript{17,21,29,30} and six were Category III observational studies\textsuperscript{31–36} (Table S1). Individual studies had low risk of bias (Table S9). However, low observational study category and heterogeneity (variable outcomes) downgraded the quality of evidence. In the previous guidelines of recording EEG\textsuperscript{17,21,29}, technical standards were based on expert opinion and not on scientific studies.

We conclude that the quality of evidence on technical EEG standards is low. Our recommendation is conditional and formulated by consensus of modified Delphi discussions. Table 3 summarizes the recommendation for technical standards.

3.2.1 Electrodes and montages
For routine EEG, the use of either gold or silver/silver-chloride cup electrodes individually applied with electrode paste or gel are suggested. Head caps are becoming more commonly used and are also acceptable if electrode impedances are checked and meet standards. Dry electrode EEG systems are not recommended yet, because they are associated with increased movement and sweat artifacts and the effectiveness of methods for mitigating this, such as automated artifact removal, have yet to be thoroughly studied\textsuperscript{34}. MRI compatible electrodes and needle electrodes are acceptable in certain circumstances. The use of the 25 electrode IFCN montage, which adds six additional subtemporal electrodes to the 10-20 array\textsuperscript{30}, is suggested to be used whenever feasible, because there is evidence that it improves the ability to detect both ictal\textsuperscript{32} and interictal\textsuperscript{37–39} epileptiform discharges. Otherwise the 10-20 array is acceptable\textsuperscript{30,32,33,35}.

One electrocardiography (ECG) channel may be used. It is also suggested to record at least two electromyography (EMG) channels if motor events of clinical interest are suspected. Two EMG channels
(if electrodes are placed on extremities bilaterally) provide an objective measurement of body movement which can be correlated to the EEG and can help in the identification of elementary motor seizure semiology (myoclonus, spasms, clonic, tonic, tonic-clonic seizures) and in the differentiation between tonic and atonic seizures. Two electrooculogram (EOG) leads may be placed in cases in which it is difficult to distinguish eye movement artifacts from slow EEG waves, and these leads should be placed according to the recommendations of the IFCN and the American Academy of Sleep Medicine—one cm lateral and above the outer canthus on the right and one cm lateral and below the outer canthus on the left.

3.2.2 Electrode impedances
It is advisable to check scalp-electrode impedance at the beginning of each EEG recording. Impedances below 100 Ω are unacceptable, as it often indicates shunting through to a salt bridge on the scalp. In order to reduce the impact of disturbances and obtain a scalp-electrode impedance lower than 5 kΩ, skin abrasion is still required, but in a small subset of cases it is not proposed. There is some evidence that a scalp-electrode impedance of 10 kΩ or higher is acceptable because modern EEG amplifiers have a relatively high input impedance. These studies have only measured EEG signal amplitude, amplitude of 60 Hz artifact, and ability to resolve evoked potentials between electrodes with varying impedances. Studies of EEG signal quality as perceived by experts in electrodes of varying impedances are lacking. Electrodes with higher impedance can be more affected by sweat, movement, and electrode pop artifact. Additionally, allowing impedance values up to 10 kΩ increases the chance that there will be a significant imbalance among the impedances of the array of electrodes. Unbalanced impedances can compromise the ability of an EEG amplifier to reject potentials that are the same at a pair of electrodes while amplifying those that are different (common mode rejection). Therefore, impedance values below 5 kΩ are suggested and an impedance value of less than 10 kΩ is considered acceptable.
3.2.3 Recording and review settings

For routine EEG in current clinical practice, frequencies of over 100 Hz are not currently considered of clinical interest. This may change in the future, with the increased use of commercial artefact reduction systems using blind signal source separation, which may work better if given EEG signals with higher signal frequency content. The Nyquist theorem specifies that the highest measurable frequency is half the sampling rate. For example, with a 256 sample/sec (Hz) sampling rate, the highest frequency that can be resolved is 128 Hz. In actuality, because of phase alignment, it is necessary to discretely sample (digitize) the signal at a rate of at least 2.5 times the highest frequency component of the signal\textsuperscript{45}. Therefore, based on the experience of experts and the frequency content of clinically relevant EEG signals, the proposed minimum sampling rate is 256 Hz.

For visualization of EEG, the suggested low-pass (high frequency) filter setting is 70 Hz and the suggested high-pass (low frequency) filter setting is 0.5 Hz. A value of 7 µV/mm is the proposed display resolution, except for children’s recordings in which 10 µV/mm is suggested. It is recommended that EEG reviewers be allowed to change the gain of channels independently, adjust time resolution, display voltage maps at a time point, add and change annotations during review, apply notch filters and adjust low-pass and high-pass filters if needed.

3.2.4 Data storage and export

We suggest archiving the entire EEG recording as well as the time-synchronized video either for the entire recording or video only from clinically relevant events. It is recommended that users be able to export EEG data for research in Comma Separated Values (CSV) or European Data Format (EDF). The International Federation of Clinical Neurophysiology is working with Digital Communication in Medicine (DICOM) to create a modern format for storage and exchange of EEG data, which will become available within the next few years\textsuperscript{46}.
3.3 Duration of recording
The database searches generated 156 articles and 19 additional articles were identified from other sources. After removing duplicates, 152 abstracts were screened. Forty-one of full text articles were assessed for eligibility. Twelve articles, three of them EEG recording guidelines, were included in qualitative analysis. PRISMA chart is included in Appendix 4C.

We identified nine eligible original research papers, two of them category I\(^{47,48}\) and seven category II-III\(^{49-55}\) observational studies. Study characteristics are summarized in Table S2. Only two Category II studies evaluated the optimal duration of sleep EEG\(^{49,52}\). All studies included QUADAS-2 domains with high risk of bias (Table S10). Most studies were at high risk of biased reference standard.

The previous consensus-based guidelines of ILAE (Commission Report Commission on European Affairs: Subcommission on European Guidelines), American Clinical Neurophysiology Society and Canadian Society of Clinical Neurophysiologists recommend of at least 20 minutes of technically satisfactory recording for routine EEG\(^{17,21,29}\) and 30 minutes for sleep EEG\(^{21}\).

A category I study in children and adults found that the sensitivity of the 15 min routine EEG compared with the 25 minute-EEG for epileptiform or non-epileptiform abnormality, was 94.1% [CI:88.7-97.4%], and the specificity 99.3% [CI:97.5 -99.9%]\(^{47}\). The sensitivity of 15 minute-EEG increased if only epileptiform abnormalities were considered (97.1% [CI: 92.6-99.2%]). Authors estimated 15-minute routine EEG to be cost effective, but recording procedure had to be rigorous to include activations, too.

In agreement, a category II study in children found that reducing the recording time of routine EEG from 20 to 15 minutes may miss epileptiform abnormalities in 2.36% [CI: 0.63–4.09%] of EEGs\(^{50}\). The largest category II retrospective study conducted in a tertiary epilepsy centre found significant decrease in the diagnostic yield for recordings shorter than 20 minutes\(^{52}\). They did not find significant difference between the yield of 20 and 30-minute routine EEG or between the yield of 30 and 60-minute sleep EEG in adult patients.
In a category I study in children and adults, in 4.5% of patients (81/1803) interictal epileptiform abnormalities became only apparent after the initial 30 minutes\(^4\). The relative increase in yield of interictal epileptiform abnormalities was 19.1% [CI: 15.6–23%]. Also, in a category II study the yield of epileptiform abnormalities was increased by 11% (p=0.001) by lengthening the recording from standard 20 to 40 minutes\(^3\). A category II study observed 51% of epileptiform abnormalities within 20 minutes of sleep-deprived EEG, 71% within 30 minutes and 93% within 90 minutes\(^4\).

3.3.1 Recommendation

The quality of evidence on optimal duration of routine and sleep EEG is low. Therefore, our recommendations are conditional. Consensus after modified Delphi discussions is to suggest the duration of 20 minutes for the routine EEG and 30 minutes for the sleep EEG (Table 3). It is advisable to book the sleep recording of infants and children in the postprandial period, where there is a higher chance to fall asleep.

We suggest individualizing the recording time and duration when increased benefit is expected\(^4,5\). Booking morning time for patients with suspected juvenile myoclonic epilepsy, prioritizing sleep recording in patients with suspected or diagnosed self-limited focal onset epilepsy of childhood or West syndrome, and on suspicion of West syndrome, extending recording at least 10 minutes after awakening to increase the probability of recording of epileptic spasms probably increase the yield of EEG.

3.4 Sleep inducing methods

The database searches generated 360 articles and 20 additional articles were identified from other sources. After removing duplicates, 259 records were screened. Sixty-nine full text articles were assessed for eligibility. Seventeen studies fulfilled the eligibility criteria and three of them were guidelines. PRISMA chart is shown in Appendix 4D.
All except one study evaluated the efficacy of sleep induction in children and young adults up to age of 18 years\textsuperscript{56}. The previous EEG recording guidelines\textsuperscript{17,21,29} do not recommend particular sleep inducing method in adults, but recommend natural sleep in children\textsuperscript{17,21} and if it fails, partial sleep deprivation or melatonin\textsuperscript{21}.

One RCT with indirectness and three category II observational studies without serious study limitations compared the yield of sleep in EEGs with partial sleep deprivation to EEGs without sleep deprivation in children and young adults (Tables S3, S11-S13). The studies did not represent all WHO regions. Burden of sleep deprivation to patient, family and society is very likely to be culturally biased. None of the studies used a stressful 24h sleep deprivation. Ten studies including six RCTs with high risk of bias and four observational studies with high risk of bias explored the sleep-inducing efficacy of melatonin or another drug (Tables S4-S6, S11-S13). The studies showed inconsistency and imprecision because of heterogeneous methods, small number of studies and small sample size in many studies. Publication bias was considered possible for 24h sleep deprivation and use of sedative drugs other than melatonin that have been used more commonly before 1990 but have been abandoned because of adverse effects.

Studies did not directly assess cost-benefit of different sleep-inducing methods, but sleep onset latency could be used as an indirect marker of cost-efficacy. Data on adverse effects of sleep-inducing methods was assessed in nine studies using sleep-inducing drugs (Tables S4-S6). However, study limitations were serious (Tables S11-S12).

3.4.1 Efficiency of sleep induction
Partial sleep deprivation was shown to increase the probability of obtaining sleep during EEG\textsuperscript{9,13,14,57} (Table S3).
A category I and a category II study showed that melatonin and partial sleep deprivation are equally efficient in inducing sleep without difference in the yield of interictal epileptiform discharges in pediatric patients\(^{58,59}\). A category II study suggested that melatonin may be more efficient in younger children aged 1-4 years in comparison to older children\(^{59}\).

A category I multicenter study found combined intervention of sleep deprivation and melatonin to be significantly more effective to induce sleep than either method alone in pediatric patients\(^{60}\). However, a smaller category I study did not find improved sleep latency when melatonin was combined with partial sleep deprivation\(^{61}\).

There was no difference in the yield of epileptiform abnormalities between the intervention groups in any of the included studies.

We also collected data on melatonin dose used in the studies. It varied from 2 mg to 10 mg. There are no trials on dose dependency for acute hypnotic or anxiolytic use of melatonin in children. In young healthy adults, increasing the dose from 1.0 to 10 mg did not significantly reduce the sleep-onset latency or the subjective sleepiness\(^{62}\). Clinical consensus recommendation by a group of European pediatric neurologists suggests a dose of 1-3 mg 30 min before the examination\(^{63}\).

There is no evidence of advantage of use of other sleep-inducing drugs than melatonin when potential benefits and adverse effects are outweighed (Tables S5-6)\(^{56,64–68}\).

### 3.4.2 Adverse effects and tolerability

Significant adverse effects of melatonin were not found in category I observational studies and randomized controlled trials that systematically assessed them in pediatric patients\(^{56,58,61,64}\). Frequency of adverse effects was higher for other sleep-inducing drugs than melatonin and their use needed safety precautions because of potential cardiovascular adverse effects and central nervous system depression (Tables S5-6). Disadvantages of sleep deprivation included difficulties to keep children awake at night
and to wake up in the morning in 50% of patients. In two studies, generalized tonic-clonic seizures occurred co-incidentally with sleep deprivation in one patient.

3.4.3 Cost-effectiveness
In a category I study, sleep latency was significantly shorter with melatonin (mean latency 21 min) compared to partial sleep deprivation (mean latency 34 min), but the result was not confirmed by another category I study. Sleep latency was also significantly reduced by combining melatonin with partial sleep deprivation in comparison to melatonin and partial sleep deprivation alone in a category I study.

3.4.4 Recommendation
We conclude that the quality of evidence on efficacy of partial sleep deprivation to induce sleep during EEG recording is moderate in children and young adults. However, it is very low for pharmacological sleep-inducing methods due to study limitations, imprecision caused by small number of studies and small sample sizes, and adverse effects. We suggest partial sleep deprivation as a primary sleep-inducing method in adults and children 12 years of age or older who can cooperate to the sleep deprivation (Table 3). Sleep deprivation is a feasible method regardless of availability of drugs and personnel needed for administration of drugs. An example of suggested partial sleep deprivation protocol is shown in Table 4. However, it is important to note that there are no studies evaluating the safety of partial or full sleep deprivation for any age group. Sleep deprivation may also cause significant distress to a child and family.

Melatonin or sleep deprivation are suggested as a primary sleep induction method in children under 12 years of age (Table 3). If sleep deprivation or melatonin fails to induce sleep, their combination may be more effective. We also propose melatonin as a primary sleep induction method in children and adults who cannot cooperate to partial sleep deprivation. The suggested dose of melatonin is 1-3
mg administered 30-60 min before the start of the EEG recording. If melatonin is not available, chloral hydrate may be used when partial sleep deprivation fails to attain sleep.

3.5 Provocative methods
The database searches generated 3483 records and 13 articles were identified from other sources. After removing duplicates, 3049 abstracts were screened. One hundred twenty-eight full-text articles were examined for eligibility. Forty-two original research studies and four guidelines\textsuperscript{17,21,29,69} were included for review. PRISMA chart is shown in Appendix 4E. Eighteen observational studies evaluated the use of hyperventilation (Table S7), 24 intermittent photic stimulation (IPS) (Table S8) and nine studies\textsuperscript{70–78} compared other provocation methods with IPS, hyperventilation and/or sleep. Part of the studies investigated several provocation methods. All studies were at high risk of bias because of limitations in both index and reference tests (Tables S14 and S15).

3.5.1 Hyperventilation
3.5.1.1 Protocol and technical standards
We found only two studies assessing hyperventilation protocol\textsuperscript{79,80}. In a category I study, 16% of seizures, 30.4% of interictal EEG abnormalities, and 30% of epileptiform discharges provoked by hyperventilation occurred during the last 2 min of the 5 min hyperventilation\textsuperscript{79}. On the other hand, 85.5% of absence seizures were elicited within 1.5 min of hyperventilation in a category III study\textsuperscript{80}. Earlier EEG guidelines recommend minimum of three minutes of hyperventilation that should be prolonged or repeated in a strong suspicion of typical absence seizures\textsuperscript{17,21,29}.

3.5.1.2 Yield of hyperventilation
We found three large category I studies that showed an additional diagnostic value of hyperventilation\textsuperscript{79,81,82}. Hyperventilation precipitated epileptiform abnormalities that were not present in a baseline EEG in 0.92% (3/326)\textsuperscript{81}, 1.1% (10/877)\textsuperscript{79} or 3.0% (95/3170)\textsuperscript{82} percentage of adult and pediatric patients. These results were supported by two Category II studies reporting epileptiform abnormalities only during hyperventilation in 0.86% (5/580)\textsuperscript{83} and 5.7% (8/141) of patients\textsuperscript{84}. In a
category III study in patients with newly diagnosed epilepsy, hyperventilation provoked epileptiform abnormalities not present in baseline in 7.7% (25/325) of patients. The yield was greatest for patients 1-19 years old (10.3%). In a study including EEGs of 100 healthy young men, no epileptiform activity was elicited by hyperventilation.

Significant increase in frequency of epileptiform discharges compared with baseline was found in of 23.7% (14/59) of patients with genetic generalized epilepsy in a category III study.

### 3.5.1.3 Safety

In a category I study assessing safety of hyperventilation, there were no significant cerebrovascular, cardiovascular or respiratory events. Seizures during hyperventilation were relatively rare. Two category I studies reported seizures that were provoked by hyperventilation in 2.2% (69/3170) and exclusively by HV in 2.9% (25/877) of patients referred to EEG on suspicion of epilepsy. Only 1/3170 patients had a generalized tonic clonic seizure. In a random sample of 580 reports of routine EEG with HV of category II study, seizures provoked by hyperventilation were reported in 2.1% (12/580) of records. Comparable or lower incidence of seizures during hyperventilation were reported in smaller category II and category III studies including narrow-spectrum studies on patients with genetic generalized epilepsy.

Three category I studies observed psychogenic non-epileptic seizures in 1.1% (10/877) and 0.9% (31/3475) of patients, and in none (0/326) during hyperventilation. A category III showed increased frequency of psychogenic non-epileptic seizures when patients were informed about a potential seizure inducing effect of hyperventilation.

### 3.5.2 Intermittent photic stimulation

#### 3.5.2.1 Protocol and technical standards

We identified only two category II and one category III studies assessing the IPS protocol. Out of 45 patients with a photoparoxysmal response (PPR), this was elicited only on eye closure during IPS in
24.4%\(^{89}\). Photoparoxysmal response occurred in 8.0% (21/263) of children, and 45% of responses were found after 9 seconds of stimulation which led to the recommendation for using 10 or more seconds for each stimulus frequency\(^{90}\). In photosensitive patients, the photosensitivity range for frequencies of 25-60 Hz was significantly higher (maximal) in the condition “eyes open with diffuser” compared with “eyes open”, and “eyes closed”, and “eye closure” (p=0.0002)\(^{91}\). Earlier EEG guidelines include the recommendation of a European expert panel on methodology of photic stimulation\(^{69}\).

### 3.5.2.2 Yield of intermittent photic stimulation

We identified one category I study that provided evidence for an additional diagnostic value of IPS\(^{92}\).

Intermittent photic stimulation revealed generalized epileptiform discharges that were not present in the EEG before stimulation in 1.5% (79/5383) of patients, and the only useful information (epileptiform discharges, epileptic or non-epileptic seizures) in 2.3% (122/5383) of patients\(^{92}\).

In line, in category II studies IPS elicited generalized epileptiform discharges (a type 4 photoparoxysmal reaction\(^{93}\)) as only epileptiform activity in 0.68% (5/732) of EEGs\(^{83}\) and epileptiform abnormalities occurring only on photic stimulation in 5.3% (12/226) of EEGs\(^{84}\). In comparison, 0.32% (44/13658) of Air Force applicants showed epileptiform abnormalities induced only on photic stimulation\(^{94}\). On the other hand, IPS provoked the only epileptiform abnormalities in 30.5% of patients with genetic (idiopathic) generalized epilepsy aged 14 – 17 years in a category III study\(^{73}\).

A category III study showed an additional yield of IPS in 3.7% (15/406) of patients with newly diagnosed epilepsy compared to baseline\(^{85}\). Repeated IPS in the second EEG after the first normal one, captured epileptiform activities in 3.0% (5/164) of patients. The yield was greatest for the patients under 20 years of age and for the patients with generalized seizures.

In a category II study, a photoparoxysmal response was found in 2.3% of 2,888 consecutive EEG recordings and in 10% of patients with epilepsy\(^{89}\).
A category III study found photosensitivity type 1 to 4 in 74% of patients with epilepsy with generalized tonic clonic seizures on awakening, in 56% in juvenile absence epilepsy, in 50% in juvenile myoclonic epilepsy, and 44% in childhood absence epilepsy compared with 23% in childhood epilepsy with centro-temporal spikes and 16% in symptomatic/cryptogenic epilepsy. The relative frequency of type 4 among all photosensitivity reactions was significantly higher in genetic generalized epilepsy (59%) than in childhood epilepsy with centro-temporal spikes (38%). In a nationwide study in Great Britain, annual incidence of patients with epilepsy and generalized spike-and-wave discharges on IPS on their first EEG was roughly 1.1 per 100,000, representing approximately 2% of all new cases of epilepsy.

3.5.2.3 Safety
In a nationwide UK category I study, 0.72% (39/5383) of patients had seizures due to IPS including a generalized tonic clonic seizure in 0.04% of patients. In 0.9% (49/5383) of patients, the IPS provoked a psychogenic non-epileptic seizure. In accordance, two category II studies reported seizures exclusively during IPS in 0.53% (1/189) and 0.68% (5/732) of patients. The intermittent photic stimulation caused epileptic seizures in 0.068% (4/5,893) of Air Force applicants, of which three out of four were generalized tonic-clonic seizures. In a category III study, the rate of psychogenic non-epileptic seizures rose significantly after informing the patients about potential seizure-inducing effects of the activations in a group of patients with only psychogenic non-epileptic seizures or with both psychogenic non-epileptic and epileptic seizures. In detail, in the informed group 17.6% (6/34) of patients showed psychogenic non-epileptic seizures due to the IPS, two thirds (4/6) of them exclusively during the IPS.

3.5.3 Other provocation methods
We did not find evidence for supporting standard use of other provocation methods than hyperventilation and IPS in routine EEG recordings. Two main indications of other provocation methods were recognized: genetic generalized epilepsies with reflex trait and focal-onset epilepsies with a specific seizure trigger. Three category III observational studies compared the provocative effect of
cognitive tasks to that of sleep deprivation, IPS and hyperventilation on interictal epileptiform discharges in juvenile myoclonic epilepsy\textsuperscript{70-72} and two in genetic generalized epilepsies\textsuperscript{73,74}. The duration of cognitive protocol was at least 15 minutes, typically over 30 minutes. The yield of cognitive tasks may exceed that of hyperventilation and IPS, but not sleep \textsuperscript{73,74}. Seizures during cognitive testing were not observed in two studies\textsuperscript{72,73} whereas they occurred in three studies\textsuperscript{70,71,74}. In patients with juvenile myoclonic epilepsy, cognitive tasks were more provocative of myoclonia than conventional methods\textsuperscript{70,71,74}.

Other category II-III studies investigated provocative effect of visual pattern stimulation in unselected patients of four to 12 years of age\textsuperscript{75} and in pediatric patients with visually induced seizures\textsuperscript{76}, and olfactory stimuli in mesial temporal lobe epilepsy\textsuperscript{77} that did not increase the diagnostic utility of routine EEG.

3.5.4 Recommendation
We conclude that the quality of evidence for hyperventilation to provoke epileptiform discharges is moderate despite study limitations (three consistent category I observational studies), but low for photic stimulation and other type of stimulations. Our recommendation was formulated by modified Delphi discussions. Summary of provocation methods in shown in Table 3. In consensus, we suggest that hyperventilation, photic stimulation including baseline recording of eyes open, and eyes closed are part of routine or sleep EEG unless contraindicated. Asking the patient to blink, close and open eyes documents artefacts and is a provocative method for eye-closure sensitivity\textsuperscript{98}. We suggest to tailor the EEG and to use other simple stimulation methods, for example touch, sudden noises or reading aloud a difficult text, when they are known to provoke seizures\textsuperscript{4}.

The patient and caregiver should be informed in advance about the potential benefits as well as adverse effects of activations, particularly seizures and potential loss of driving permission.
Information may also increase the occurrence of non-epileptic seizures. Patient has the right to know about the possibility to refuse activations.

The EEG technician is responsible for the safety of the patient and the quality of recording that necessitates continuous monitoring of one recording at a time. Patient should not be left alone for any moment or left under observation of parent/guardian for more than a few minutes. During seizures, it is advisable to test the patient with a standardized method. We suggest to use simplified versions of the ILAE guideline and UK national guideline for testing patients during seizures in long-term video EEG (Table 5)\textsuperscript{99,100}. For testing of a potential absence seizure during generalized spike-and-wave discharge longer than 3-4 seconds, we suggest the method proposed by the ILAE Neurophysiology Task Force “The role of EEG in the diagnosis and classification of the epilepsy syndromes: a tool for clinical practice”\textsuperscript{4}. EEG technician gives simple commands or words when the generalized discharge starts and continues during the length of absence. Patients are monitored for a spontaneous response and after the offset of discharge asked what they were told.

In adults, we suggest to perform IPS before hyperventilation at the beginning of EEG at least 3 minutes apart\textsuperscript{69}. However, if the referral diagnosis is genetic generalized epilepsy, it is advisable to do activations at the end of recording due to increased probability of seizures. IPS often raises level of vigilance and decreases probability of sleep and hyperventilation has an opposite effect\textsuperscript{101}. Therefore, in children, we suggest performing hyperventilation at the beginning of sleep EEG and IPS at the end.

3.5.4.1 Hyperventilation protocol
The patient is instructed to breathe deep 15-30 times/minute at least three minutes. In children, a windmill is useful to enhance breathing. In some patients, numbness or tingling of perioral region and fingers may occur; if so, this is not a reason to discontinue hyperventilation. The EEG technician should encourage the patient and rates breathing effort adequate or inadequate. It is preferable to record two minutes of awake EEG after hyperventilation in all patient groups.
Contraindications for hyperventilation are sickle cell disease or trait, Moya-Moya disease and syndrome, cerebrovascular malformations including aneurysms, cerebrovascular events in the last three months, raised intracranial pressure, myocardial infarction, cardiac arrhythmias and other severe forms of cardiac disorders, severe pulmonary disorders, and pregnancy. Preferably, list of contraindications is available for the referring physician to report existing contraindication. As a minimum and in cases of a time lag between referral and EEG, EEG technician should inquire the patient about contraindications and document the answer.

3.5.4.2 Intermittent photic stimulation protocol
We suggest to perform the IPS in accordance with the ILAE guideline on revisited methodology of photic stimulation in EEG recording. There is no need to repeat IPS during the same EEG recording if it remains unequivocal. Contraindication for the IPS is pregnancy due to high risk of seizure.

3.6 Conclusions
Routine and sleep EEG have an established role in clinical diagnosis of epilepsy. However, the overall quality of evidence for recording standards of routine and sleep EEG is low, which is an important limitation. This paper summarizes the available evidence and provides expert consensus-based standards to record EEG. Although the recommendations are conditional, they provide a feasible standard for new EEG laboratories and challenge established EEG laboratories to evaluate their protocols. In the future, further research development and diagnostic accuracy studies are needed.

Disclosure of Conflicts of Interest
Sándor Beniczky has served as scientific consultant for Epihunter and received speaker honoraria from Natus. Jonathan J. Halford has served as a Board Advisor for CortiCare. Ronit M. Pressler has given lectures for NATUS. The remaining authors have no conflicts of interest.
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**Table 1.** Clinical questions and PICO statements.

<table>
<thead>
<tr>
<th>Question</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. What are the indications for routine and sleep EEG?</td>
<td>Patient in EEG</td>
<td>EEG recording</td>
<td>No EEG recording</td>
<td>Impact on diagnostics, management decisions or prognostication</td>
</tr>
<tr>
<td>2. What are the minimum technical standards for routine and sleep EEG?</td>
<td>Not practically applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. What provocation methods should be used in routine and sleep EEG and how?</td>
<td>Patient in EEG</td>
<td>Photic stimulation, Hyperventilation, Other provocation</td>
<td>No provocation</td>
<td>Epileptiform abnormality, Seizure -epileptic, -non-epileptic, Adverse effects</td>
</tr>
<tr>
<td>4. What should be a minimum duration of routine and sleep EEG to be optimally diagnostic?</td>
<td>Patient in EEG</td>
<td>EEG duration 1</td>
<td>EEG duration 2</td>
<td>Abnormal EEG finding</td>
</tr>
<tr>
<td>5. Should sleep deprivation (partial or all night/24h) used to obtain sleep?</td>
<td>Patient in EEG</td>
<td>Sleep deprivation</td>
<td>Natural sleep</td>
<td>Sleep, Adverse effects, Cost-benefit</td>
</tr>
<tr>
<td>6. Can melatonin or other drugs be used for sleep induction?</td>
<td>Patient in EEG</td>
<td>Melatonin, Other sleep-inducing drug</td>
<td>Sleep deprivation, Sleep inducing drug</td>
<td>Sleep, Adverse effects, Cost-benefit</td>
</tr>
</tbody>
</table>

**Table 2.** Indications of non-emergent EEG recorded by appointment

<table>
<thead>
<tr>
<th>Epilepsy-related indications</th>
<th>Other indications for differential diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical suspicion of seizure or epilepsy</td>
<td>Psychogenic non-epileptic seizures</td>
</tr>
<tr>
<td>Reconsideration of the initial diagnosis of epilepsy</td>
<td>Paroxysmal behavioral changes</td>
</tr>
<tr>
<td>Syndromic classification of epilepsy</td>
<td>Suspected encephalopathy</td>
</tr>
<tr>
<td>Changes in seizure pattern</td>
<td>Acute or subacute dementia</td>
</tr>
<tr>
<td>Etiological evaluation of epilepsy</td>
<td></td>
</tr>
<tr>
<td>Prior to tapering of AED in seizure free patients</td>
<td></td>
</tr>
<tr>
<td>Systematic follow up of specific epileptic syndromes (for example West syndrome and Epileptic encephalopathy with continuous spike-and-wave during sleep)</td>
<td></td>
</tr>
</tbody>
</table>
Table 3. Summary of minimum standards for recording routine and sleep EEG

| Electrode types                  | Gold or silver/silver-chloride cup electrodes applied with electrode paste or gel, electrode caps, MRI compatible electrodes and needle electrodes in certain circumstances |
| Electrode array                  | The 25-electrode IFCN montage, when possible. Otherwise: 10-20 array. |
| Polygraphic channels             | One ECG At least two EMG channels if motor events of clinical interest are suspected At least two EOG channels if assistance is needed in differentiation between eye movement and slow EEG activity |
| Electrode impedances             | < 5 kΩ is recommended < 10 kΩ is considered acceptable |
| Minimum sampling rate            | 256 Hz |
| Filtering (EEG)                  | High pass 0.5 Hz; Low pass 70 Hz |
| Filtering (EOG)                  | High pass 0.3 Hz; Low pass 35 Hz |
| Filtering (EMG)                  | High pass 10 Hz; Low pass 100 Hz |
| Display                          | Resolution 7 µV/mm for adults’ EEG, 10uV/mm for children’s EEG Possibility to adjust viewing settings, gain of each channel, time resolution, filters and annotations Possibility to display voltage maps |
| Data storage                     | The entire EEG and video from clinical events |
| Data export                      | Comma Separated Value data format (CSV) or European data format (EDF) or Digital Communication in Medicine (DICOM) format |
| Duration of recording            | Routine EEG 20 min Sleep EEG 30 min To note: - individualize the sleep EEG recording time and duration when increased benefit is expected - postprandial period increases the chances of sleep in infants and children |
| Sleep induction                  | Partial sleep deprivation for adults and children ≥ 12 years of age Melatonin or sleep deprivation in children < 12 years of age Dose of melatonin: 1-3 mg administered 30-60 min before EEG recording. If melatonin is not available, chloral hydrate may be used when partial sleep deprivation fails to attain sleep. |
| Hyperventilation (HV)            | At the beginning of routine or sleep EEG ≥ 3 min after IPS. Exceptions: if EEG indication is genetic generalized epilepsy, 15-30 deep breaths /min for ≥ 3 min To note: - checklist for contraindications - testing during seizure |
perform HV at the end of recording

<table>
<thead>
<tr>
<th>Method</th>
<th>At the beginning of routine or sleep EEG ≥ 3 min before HV. In children, perform IPS at the end of sleep EEG.</th>
<th>Method: ILAE guideline on revisited methodology of photic stimulation*</th>
<th>To note:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermittent photic stimulation (IPS)</td>
<td></td>
<td></td>
<td>- contraindication pregnancy</td>
</tr>
<tr>
<td>Asking the patient to blink, close and open eyes</td>
<td>At the beginning of routine EEG In wake period at the end of sleep EEG (assessment of posterior dominant rhythm)</td>
<td>To note:</td>
<td>- testing during seizure</td>
</tr>
<tr>
<td>To note:</td>
<td>- assisted eye closure may be needed in children</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


**Table 4. Suggested partial sleep deprivation protocol for sleep EEG in morning time**

<table>
<thead>
<tr>
<th>Age group</th>
<th>Children aged &lt; 6 year</th>
<th>Children aged 6-12 years</th>
<th>Children aged &gt;12 years</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Instructions</td>
<td>Shorten the sleep by 1-3 hours or an amount that you estimate is necessary for falling asleep at the time of EEG.</td>
<td>Go to sleep two hours later than usual and wake up two hours earlier than usual. Stay awake until the EEG.</td>
<td>Go to sleep two hours later than usual, but at the latest at 00 AM. Stay awake from 04 AM until the EEG.</td>
<td>Go to sleep at 00 AM. Stay awake after 04 AM until the EEG.</td>
</tr>
</tbody>
</table>

**Table 5. Suggested protocol for testing patients during seizures in routine and sleep EEG**

<table>
<thead>
<tr>
<th>Children &lt; 6 years old</th>
<th>Children ≥ 6 years old and adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Say the patient’s first name</td>
<td>1. Say the patient’s first name</td>
</tr>
<tr>
<td>2. “Are you ok?”</td>
<td>o If reacting, ask: “What do you feel?”</td>
</tr>
<tr>
<td>3. “Lift both arms up/like Superman or touch toy with right &amp; left hand/ clap.”</td>
<td>o If not, touch arm</td>
</tr>
<tr>
<td>o First say only, if not reacting show</td>
<td>2. “Lift arms.”</td>
</tr>
<tr>
<td>4. Postictally ask: “Did you know what just happened?”</td>
<td>o First say only, if not reacting show</td>
</tr>
<tr>
<td>3. “Please repeat and remember the following words: horse, table (for example)”</td>
<td>3. “Please repeat and remember the following words: horse, table (for example)”</td>
</tr>
<tr>
<td>4. Postictally ask: “Did you have a seizure?”</td>
<td>“Can you describe what happened?”</td>
</tr>
<tr>
<td>“What did you feel right before/at the beginning of the event?”</td>
<td>“Can you recall the words I said to you/what I asked to do?”</td>
</tr>
</tbody>
</table>

3.7 References


16. WHO. Laboratory Quality Management System: handbook [Internet]. 1.1. Lyon: WHO Library


