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Guidelines of the International Headache Society for clinical trials with neuromodulation devices for the treatment of migraine

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Abstract

Background: Although the European Medicines Agency and the US Food and Drug Administration have cleared several devices that use neuromodulation to provide clinical benefits in the acute or preventive treatment of migraine, the Clinical Trials Committee of the International Headache Society has not developed guidelines specifically for clinical trials of neuromodulation devices. In recognition of the distinct needs and challenges associated with their assessment in controlled trials, the Committee provides these recommendations for optimizing the design and conduct of controlled trials of neuromodulation devices for the acute and/or preventive treatment of migraine.

Methods: An international group of headache scientists and clinicians with expertise in neuromodulation evaluated clinical trials involving neuromodulation devices that have been published since 2000. The Clinical Trials Committee incorporated findings from this expert analysis into a new guideline for clinical trials of neuromodulation devices for the treatment of migraine.

Results: Key terms were defined and recommendations provided relative to the assessment of neuromodulation devices for acute treatment in adults, preventive treatment in adults, and acute and preventive treatment in children and adolescents. Ethical and administrative responsibilities were outlined, and a bibliography of previous research involving neuromodulation devices was created.

Conclusions: Adoption of these recommendations will improve the quality of evidence regarding this important area in migraine treatment.

Keywords

Migraine, devices, neuromodulation, recommendations

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Introduction

The Clinical Trials Committee of the International Headache Society has a long-standing history developing guidelines for clinical trials of primary headache disorders, including migraine. Current publications that provide guidance for clinical trials on drugs in adults with migraine include those for the acute treatment of migraine and the preventive treatment of chronic and episodic migraine (1–3). Guidelines are also available for children and adolescents for the preventive treatment of migraine (4).

Recent years have witnessed an increasing interest in and testing of neuromodulation devices for the therapeutic approach of primary headaches, particularly migraine and cluster headache. The European Medicines Agency and US Food and Drug Administration have recently cleared several devices based on the principles of neuromodulation for the acute or preventive treatment of migraine. Both agencies have established processes for the evaluation and clearance of medical devices (5,6), and the evidence-based expansion of the neuromodulatory class of treatments is a promising development for clinicians and their patients with migraine. However, because the supporting data required for clearance depends on the classification of the device being considered for clearance (7,8), clinical trials evaluating them use different designs, trial populations, and efficacy outcomes (9), which complicates the interpretation of results and limits their translational utility.

The device-specific methodological challenges and inconsistency of evidence supporting the efficacy and safety of neuromodulation devices in migraine has heightened the need for guidance. Based on findings from a subject matter expert review of clinical trials published in the past 20 years (Table e-1 and Table e-2 in the Supplementary Material), as well as recommendations from existing guidelines for clinical trials for acute and preventive treatments of migraine (1–4), this guideline proposes standardized approaches to the assessment of neuromodulation devices intended for the acute and preventive treatment of migraine for adults and children/adolescents. To facilitate consultation, its recommendations are presented mostly in tabular format.

1. Definitions

Please also see Table 1 for the full list of definitions of terms used in this manuscript.

1.1 Medical device

The European Union (5) defines a "medical device" as any instrument, apparatus, appliance, software, implant, reagent, material, or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes:

- Diagnosis, prevention, monitoring, prediction, prognosis, treatment, or alleviation of disease
- Diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability
- Investigation, replacement, or modification of the anatomy or of a physiological or pathological process or state

The authorised purposes of a medical device also include providing information by means of in vitro examination of specimens derived from the human body that does not achieve its principal intended action by pharmacological, immunological, or metabolic means, in or on the human body, but which may be assisted in its function by such means (5).

1.2 Neuromodulation device

A neuromodulation device is defined as any medical device that modulates the activity of the brain, the spinal cord, or peripheral nerves by means of electricity, magnetic fields, or other device-mediated modalities to either inhibit or facilitate neural impulses to achieve a clinical benefit for patients. This definition excludes devices for delivering medications, as their principal mode of action is associated with the drug, not the device. Trials using devices for drug delivery should follow the guidelines for clinical trials of pharmaceuticals (1–4).

2. General recommendations

Whenever possible, clinical trials for neuromodulation devices in migraine should follow the recommendations shown in Table 2, many of which have been adapted from the clinical trial guidelines for pharmaceuticals (1–4). Recommendations about the use of controls in clinical trials of neuromodulation devices are presented in Table 3.

2.1 Trials for the acute treatment of migraine in adults

Recommendations for trials of neuromodulation devices in the acute treatment of migraine in adults are shown in Table 4. Most of these recommendations align with the guidelines for controlled trials of acute treatment of migraine attacks in adults (1). Refer to that publication (1) for more information regarding specific items in Table 4.

Table 1. Definition of terms used in the manuscript.

DEFINITION	REFERENCE PAGE
Freedom from the most bothersome symptom: absence of the most bothersome migraine-associated symptom at a prespecified time after treatment (e.g. 2 hours, 24 hours). See also below: *Most bothersome symptom*	Diener et al. Cephalalgia 2019; 39: 694
Headache intensity: a measure of pain intensity that can be scored on a 4-point scale (where 0=no headache and 3=severe headache), a 100-mm visual analogue scale, or an 11-point numerical rating scale	Diener et al. Cephalalgia 2019; 39: 695
Meaningful relief: a trial subject's perception that an intervention has had positive effects on migraine headache pain and/or associated symptoms	Diener et al. Cephalalgia 2019; 39: 696
Moderate/severe headache day: a 24-hour period with headache pain of moderate or severe intensity that lasts at least 4 hours without medication, or a day with a headache pain of at least moderate intensity that responds to acute treatment with a migraine-specific medication	Tassorelli et al. Cephalalgia 2018; 38: 810 Diener et al. Cephalalgia 2020; 40: 1035 Abu-Arafeh et al. Cephalalgia 2019; 39: 810
Migraine attack: a medical episode involving the symptoms of migraine described in the current edition of the International Classification of Headache Disorders. In clinical trials, a migraine attack interrupted by successful treatment, sleep, or temporary remission that recurs within 48 hours is considered a single attack, as are attacks lasting more than 48 hours	Diener et al. Cephalalgia 2020; 40: 1035-36
Migraine day: a 24-hour period with headache lasting at least 30 minutes without intake of analgesics and meeting the current edition of the International Classification of Headache Disorders criteria for migraine or probable migraine; may also signify a day with headache that successfully responds to acute treatment with a migraine-specific medication (e.g. ergotamine, triptan, ditan, gepant)	Diener et al. Cephalalgia 2020; 40: 1035
Most bothersome symptom: The most bothersome symptom associated with a migraine attack that is not a feature of the headache (e.g. nausea, vomiting, phonophobia, photophobia); also an endpoint developed to align trial outcomes with the symptom(s) of importance to people with migraine. In migraine clinical trials, subjects can identify the most bothersome symptom that has typically affected them in the past (e.g. at the baseline visit) or the most bothersome symptom at the time of the qualifying attack but before the intervention is administered	Diener et al. Cephalalgia 2019; 39: 694
Pain freedom: complete disappearance of pain at a given time point after the delivery of the experimental intervention and before the use of rescue medication or additional experimental interventions (e.g. 2 hours, 24 hours, 48 hours)	Diener et al. Cephalalgia 2019; 39: 694
Pain relief (or headache relief): a reduction in headache pain intensity from moderate or severe at baseline to mild or none at a given time point after treatment and before the use of rescue medication or additional experimental interventions (e.g. 2 hours, 24 hours, 48 hours)	Diener et al. Cephalalgia 2019; 39: 694
Relapse: the occurrence of headache pain of any intensity within 24 or 48 hours (as pre-specified in the protocol) after treatment in a subject who was pain-free 2 hours after the initial intervention	Diener et al. Cephalalgia 2019; 39: 694
Responder rate: the percent change from baseline in the number of migraine days or number of moderate/severe headache days in each dosing interval; the responder rate threshold, usually set at 50%, must be prospectively defined	Tassorelli et al. Cephalalgia 2018; 38: 810 Diener et al. Cephalalgia 2020; 40: 1035 Abu-Arafeh et al. Cephalalgia 2019; 39: 810
Sustained pain freedom: pain freedom achieved at 2 hours after treatment that is maintained through 24 or 48 hours (as pre-specified in the protocol) without use of rescue medication or additional experimental interventions	Diener et al. Cephalalgia 2019; 39: 695
Time to meaningful relief: the interval between the administration of treatment and a trial subject's perception that an intervention has had positive effects on migraine headache pain and/or associated symptoms; in clinical trials, meaningful relief should be assessed using electronic diaries with time-stamp capabilities.	Diener et al. Cephalalgia 2019; 39: 696

(continued)

Table 1. Continued.

DEFINITION	REFERENCE PAGE
This is usually calculated from the end of treatment delivery. Other options apply in case of long-lasting procedures and are acceptable as long as they specified *a priori*	
Time to pain freedom: the interval between the administration of treatment and a trial subject's perception of no migraine headache pain; typically calculated using a survival analysis at time points earlier than 2 hours after treatment	Diener et al. Cephalalgia 2019; 39: 696
Total freedom from migraine: the absence of migraine-related pain, nausea, vomiting, photophobia, and phonophobia at the primary efficacy time point (i.e. 2 hours after treatment in most acute trials)	Diener et al. Cephalalgia 2019; 39: 695

2.2 Trials for the preventive treatment of migraine in adults

Recommendations for trials of neuromodulation devices in the preventive treatment of migraine in adults are presented in Table 5. Unlike clinical trials of medications for the preventive treatment of migraine, which use different designs to evaluate subjects with episodic migraine and chronic migraine (2,3), clinical trials of neuromodulation devices can combine these populations (Table 2). This consideration is based on the fact that episodic and chronic migraine differ in terms of comorbidity, need for concomitant medications and use of acute medications, but the potential of neuromodulation devices to interfere with concomitant treatments or associated comorbidities is very limited. Refer to those guidelines (2,3) for more information regarding the categories discussed below.

2.3 Trials for the preventive treatment of migraine in children and adolescents

Recommendations for clinical trials of neuromodulation devices in the treatment of migraine in children and adolescents are shown in Table 6. As with the recommendations for adult populations, these recommendations largely align with current guidance for clinical trials of pharmaceuticals in children and adolescents with migraine (4). Refer to that guideline for more information regarding the recommendations in Table 6.

3. Steering committee

Neuromodulation devices for the treatment of patients with migraine tend to be developed by researchers who may not have expertise in the field. For trials sponsored by industry, a Steering Committee that includes academics with an expertise in Headache Medicine, biostatisticians, and (if appropriate) company representatives should be formed. For investigator-initiated trials (i.e. developed and sponsored by independent investigators or academics), a Steering Committee is unnecessary. Whether or not a committee is formed, investigators and sponsors are responsible for all aspects of a clinical trial, including conception; design; operational execution; data handling; data analysis and interpretation; subsequent reporting and publication; and compliance with all local laws and regulations.

4. Independent data safety monitoring board

An independent data safety monitoring board and predefined stopping rules for futility or safety are recommended in case of prior knowledge or strong suspicion that a device under consideration has the potential to harm patients (e.g. when serious side effects were reported in proof-of-concept studies). Independent interim analysis by the data safety monitoring board should be considered for assessment of the pre-defined stopping rules.

5. Trial registration

Prior to the initiation of a trial, registration is necessary at clinicaltrials.gov, clinicaltrialsregister.eu, anzctr.org.au, or a similar regional or national official database.

6. Publication

A publication committee should be formed prior to the start of the trial. Before a trial is initiated, investigators and sponsors (if applicable) should agree upon timelines for publication; ideally, estimated publication dates be included in the protocol. All research results — primary and secondary endpoints and all safety data, either positive or negative — must be published in manuscript form; at the time of trial initiation or at the end of recruitment, a design paper with baseline data may be published. Authorship should be based on the recommendations of the International Committee of Medical Journal Editors (21).

Table 2. General recommendations for clinical trials of neuromodulation devices for the treatment of migraine.

	Recommendations	Comments
Subject Selection		
Migraine definition	• Eligible subjects should fulfil the diagnostic criteria for migraine in the most recent version of the ICHD (10) • Subjects fulfilling criteria for chronic or episodic migraine may be included in trials for the acute or preventive treatment of migraine	• Trials for the acute and preventive treatment of migraine can include subjects with episodic or chronic migraine • Due to the favorable safety profile of non invasive neuromodulation, trials dealing with this type of treatment may also include patients with a higher headache burden who may not qualify for inclusion in drug trials due to the need of concomitant medications or because of the presence of multiple comorbidities • Due to the higher risk associated with invasive neuromodulation, specific eligibility criteria should be adopted to target subjects for whom the benefit/harm ratio justifies the trial (e.g. refractory migraine)
Other primary headaches[a]	• Subjects with other concomitant primary headache types (e.g. tension-type headache) are allowed if attacks are infrequent ($<$1 day/month and $<$12 days/year) and subjects can clearly differentiate them from migraine attacks based on the quality of pain and associated symptoms • When trials target subjects with chronic migraine, individuals with more frequent attacks of tension-type headache may be enrolled as long as they can clearly discriminate between the two types of primary headache and/or an ad hoc diary is used to capture the different types of headache (1)	
Secondary headaches[a]	• Subjects with a history of secondary headache should be excluded • Medication-overuse headache represents an exclusionary criterion when the pre-existent headache disorder is not migraine and the subject does not fulfil ICHD criteria for chronic migraine • Subjects with chronic migraine and acute medication overuse (i.e. intake of simple analgesic(s) for $\geq$15 days/month or intake of migraine-specific drugs, alone or in combination with analgesics or opioids, on $\geq$10 days/month) are eligible for enrolment in trials targeting chronic migraine, but it should be clearly indicated which subjects are with and without medication overuse (1,2)	
Age at onset[a]	Age at onset of migraine should be $<$50 years (1)	
Age at entry	• For adults, the range 18-70 years of age is recommended (1,2) • Individuals in higher age groups may be considered for inclusion in trials using non-invasive neuromodulation based on an	For trials involving adults (aged $\geq$18 years): • The inclusion of subjects $>$70 years is encouraged in post-approval studies (1)

(continued)

Table 2. Continued.

	Recommendations	Comments
	increased safety margin with this type of devices, although those older than age 70 years are at increased risk of serious adverse outcomes (stroke, myocardial infarction, cardiac arrhythmia, death) that may be completely unrelated to treatment, thus increasing the possibility that confounding variables will influence results • For trials involving children and adolescents, subjects aged 6-11 years should be classified as children, and subjects aged 12-17 years should be classified as adolescents (4)	• As medical devices are less likely to cause drug-drug interactions, medical device trials can safely assess older populations than drug trials • Because older patients often have co-morbidities and use concomitant therapies that can interact with the investigational device and affect performance, analyses should plan accordingly (11)
Duration of migraine[a]	• In adults, migraine should have been present for $\geq$12 months (1) • In children and adolescents, migraine should have been present for $\geq$6 months (4)	
Sex[a]	• Males and females with migraine are eligible to participate in clinical trials, ideally in a distribution that reflects the sex ratio of population being studied • Whenever possible, evaluate sex differences in treatment response using pre-specified or post-hoc analyses • In female subjects, performing a secondary analysis for attacks related and not related to menstruation is advisable (1)	
Concomitant drug use	• The treatment of concomitant and comorbid conditions may be permitted with precautions and can be considered more liberally in device trials than in drug trials due to lack of off target side effects • If allowed, treatment for concomitant and comorbid conditions should have been stable for at least 3 months and remain stable across the trial duration • The following should not be permitted: current use of opioids for >2 days/month; botulinum toxin injections or calcitonin gene-related peptide inhibitors in the past 6 months (12) • Overuse of medications for the acute treatment of migraine (as defined in ICHD (10)) should be an exclusionary criterion unless the trial is designed to assess: o Subjects with chronic migraine o The effects of neuromodulation on medication overuse	• Unlike drug trials, the use of concomitant medications that are not expected to influence trial results is generally acceptable in neuromodulation device trials due to a minimized risk of drug-drug interactions
Study Design		
Study center[a]	• Pilot clinical trials may represent a useful starting point for probing the initial feasibility of a new device, but they are not sufficient to establish definitive efficacy (13) • An adequately powered, multi-center study should be performed in pivotal trials to demonstrate consistent tolerability	

(continued)

Table 2. Continued.

	Recommendations	Comments
	(the degree to which overt AEs can be tolerated); safety (risks assessed by laboratory testing, physical exam, clinical AEs, and other tests); and efficacy of an investigational device (13)	
Training	• The safe and correct use of a device represents a specific requirement for most neuromodulation devices • Sponsors should ensure that investigators have or receive the appropriate amount of training and experience necessary for the safe and effective use (2,13) • In the case of self-use devices, subjects should be: o Appropriately trained by expert personnel o Provided with instructions for use to review at home, such as online video tutorials and other training materials specific to the device	• Invasive neuromodulation devices require appropriate and certified training for the operators • Continued training may be needed as part of clinical study plan to facilitate safe use of the device • For self-administered stimulation, device familiarity and user knowledge is important to properly test the efficacy of the device and to minimize side-effects • Use of devices requires more patient interaction than a drug, so training is essential
Blinding	• For most devices, blinding represents a significant challenge due to an active signal, but strategies to enhance and preserve blinding should be used whenever possible • In the case of self-managed devices or if adjustments for true or sham stimulation are needed, a device trainer may be unblinded to provide participants with instructions specific to the assigned device or a third investigator that is unblinded can be involved, but those trusted third parties should have no further interaction with participants to allow for investigators and participants to remain blinded to treatment assignments throughout the study (12) • Successful blinding should be assessed at the end of the study (see blinding assessment)	• In cases where blinding the subject and/or investigator is not possible, it may still be possible and is strongly recommended that independent, third-party evaluators of clinical measurements and/or endpoints be blinded to the intervention assignment (13) • In circumstances when blinding throughout the entire study is not possible, the following can implemented to minimize bias (13): o Subjects and study staff should be blinded to intervention assignments until after a potential subject has been screened and has completed enrolment o Subjects should be blinded until after randomization to avoid issues with differential dropout that may be related to knowledge of the intervention assignment o More objective endpoints that are relevant for the clinical outcome should be adopted whenever possible in addition to subject's reported outcomes o In cases in which subject-reported outcomes are utilized, measurements should occur when no clinical staff associated with the investigation are present o A script should be drafted for clinical staff to use to standardize the follow-up questions o Subjects included in the study have to state that they will refrain from consulting any media or web content related to the type of stimulation they receive, and should not be in contact with other patients participating in the same or similar studies

(continued)

Table 2. Continued.

	Recommendations	Comments
		o Prioritize the inclusion of subjects naïve to any type of neuromodulation
Controls	• Interventions under evaluation in pivotal trials for neuromodulation devices of migraine should be compared with one of the controls listed in Table 3 (1,13) • Because there is less bias associated with study designs that use concurrent controls than with those that use non-concurrent controls, use of a concurrent control is highly recommended (13)	• Use of a control for devices presents with specific challenges not encountered with drug trials • The placebo effect introduces a bias into the comparison of improvement from an investigational device relative to a control; for this reason, it is mandatory to include a placebo control whenever possible to compare the investigational device to a therapy that is deemed ineffective (13) • Each type of control has advantages and limitations for use in a clinical study, and the control ultimately chosen should be the one that best reflects the study's design (13) • Table 3 also lists controls that are not considered adequate for the evaluation of the efficacy of neuromodulation devices
Design types	• Pivotal comparative studies should preferably utilize parallel-group design • Add-on trials are also applicable, especially in subjects with a high burden of disease or who have responded poorly to previous drugs treatments • Combined double-blind trials that evaluate the efficacy of a device in the acute and the preventive treatment of migraine are possible once the device has proved to be effective in both indications separately	• Parallel group designs are preferential to paired or cross-over designs • Paired and crossover designs may be challenging with devices because the type of signals between the active and placebo device may be too easily differentiated by the subject • Some neuromodulation devices have demonstrated efficacy as acute and preventive treatments (13)
Randomization[a]	In pivotal studies, subjects should be randomized (1)	
Stratification[a]	• When a decision is made to study important subgroups or strata (i.e. multiple centers, covariates considered highly predictive of subject outcomes [the presence or absence of co-morbidities, concomitant drug use] stratified randomization in which randomization occurs separately in each of the pre-specified strata) should be considered (2,13) • Stratifying by age (e.g. 65-74 years, $\geq$75 years) can also be considered based on relevant disease characteristics (11)	
Intention-to-Treat/modified Intension-to-Treat	• Randomized controlled trials should follow the principles of intention-to-treat, when possible • The full analysis set may be modified to exclude subjects from the analysis if no treatment was taken, if no data points after randomization were recorded, or if compliance with the use of the device was inconsistent (1)	• A modified intension-to-treat population may be used in specific cases to exclude subjects who (14): o Were deemed ineligible after randomization o Never started treatment o Used it inappropriately

(continued)

Table 2. Continued.

	Recommendations	Comments
Duration of the study[a]	For trial assessing the preventive efficacy of a device: • A minimum 28-day prospective baseline period, and 12-week double-blind treatment period is recommended • Treatment periods longer than 12 weeks can be used to evaluate cumulative benefit or persistence of efficacy and collect additional safety and tolerability data For trial assessing the acute efficacy of a device: • A minimum 28-day prospective baseline period is recommended • The duration of double blind period depends on the numbers of attacks that need to be treated. It should be generally limited to 4 weeks for trial addressing only one attack, while it may be extended to 6-8 weeks in trials evaluating the consistency of response across multiple attacks.	• Mixed trials with a double-blind phase followed by an open-label period provide useful information on different aspects of the intervention regarding: • Efficacy — persistence, consistency, improved familiarity with the device, effect on acute treatments • Usability —in case of self-administered devices • Safety
Result Evaluation		
Statistics[a]	• The following should be prospectively defined in a pre-planned analysis of the data: o Primary, secondary, and exploratory outcomes o Modalities of data collection o Statistical analysis plan o Multiple-testing procedure o Sample size needed for statistical significance o Analysis populations o Rules for imputation of missing data o Methods for comparing the baseline and treatment phases and treatment groups (3)	
Monitoring	• Headache-related variables and the use of acute medications is captured with diaries, possibly using electronic versions that can produce time stamps • For other endpoints, the use of validated tools, whenever available, is recommended	• Whenever possible, electronic diaries should be used, as they provide optimal modalities to prospectively record data and monitor compliance.
Adverse events[a]	• Documentation of adverse events (AEs) and serious AEs during treatment should follow local institutional review board requirements and the guidelines of regulatory authorities and Good Clinical Practice (3,15) • Acceptable methods of documentation include lists of AEs, spontaneous reports, recordings, open-ended questions (if the event is not covered by the AE listing), and direct questioning (3) • Report AEs separately for active treatment and placebo (3) • For implanted devices a long term follow-up (several months-years) is recommended	• Previous clinical experiences with invasive neurostimulation suggest the importance of monitoring implanted subjects over a long period

(continued)

Table 2. Continued.

	Recommendations	Comments
Blinding assessment	Because blinding can be challenging for neuromodulation devices, it is important to gauge how successful blinding is in the trial for both subjects and investigators.	The quality of blinding can be assessed with questionnaires; indices are available for the analysis of results (1) (e.g. James' Index or Bang Index (16) (17))
Other		
Participation in multiple trials[a]	• Subjects may not participate in more than one clinical trial at the same time; an (e.g. open-label phase of a long-term safety trial) should be counted as part of a single trial • Subjects should not participate in more than one trial assessing the same treatment	—

ICHD, International Classification of Headache Disorders.
[a]Recommendations coincide with current recommendations for clinical trials of pharmaceuticals; for more information, refer to Diener et al., 2019; Tassorelli et al., 2018; Diener et al., 2020; Abu-Arafeh et al., 2019 (1–4).

7. Ethics

All clinical trials must follow standardized ethical and safety guidelines, and they must be approved through appropriate Institutional Review Boards or Ethics Committees. In trials involving children and adolescents, participants must provide informed assent, and parents or guardians must provide informed consent. Trials must be conducted in accordance with the Declaration of Helsinki (22) and Guideline for Good Clinical Practice (15), and they must follow the rules of local regulatory authorities (5,6).

8. Conflicts of interest

To maintain the credibility of a trial, authors must declare their conflicts of interest in trial-related publications. A conflict of interest exists whenever professional judgment concerning a primary interest (e.g. subject wellbeing or the validity of research) may be influenced by a secondary interest (e.g. financial relationship to a trial sponsor). Financial relationships that represent potential conflicts of interest include employment, consultancies, research grants, fees and honoraria, patents, royalties, stock or share ownership, and paid expert testimony. Note that conflicts of interest extend to an investigator's immediate family (i.e. partner and children). Investigators should avoid entering into agreements with sponsors, both for-profit and non-profit, that restrict access to study data, limit its analysis and interpretation, or interfere with the independent preparation and publication of manuscripts.

9. Post-approval registries

The IHS recommends post-approval product registries (i.e. prospective open-label observational studies) to evaluate the use of newly-cleared devices in clinical practice. Registries generate real-world data on long-term efficacy, tolerability, and safety. They also measure compliance and adherence. Registries may also yield insights about individuals with migraine who have coexistent or comorbid conditions (e.g. chronic pain syndromes, cardiovascular disease) that disqualified them from clinical trials.

10. Health technology assessment

Health technology assessments seek to provide policy makers with information on the clinical and economic value of health technologies (including medical devices) and organizational systems used in health care to inform their reimbursement or coverage decisions (23,24). The assessment of medical devices poses different challenges from those of pharmaceuticals.

Table 3. Concurrent and non-concurrent controls for clinical trials of neuromodulation devices for the treatment of migraine. Adapted from reference 13.

	Description	Comments
Concurrent — Recommended		
Active intervention control (i.e. active)	Control group uses or is exposed to another intervention that delivers a known effect	• Demonstration of either superiority or non-inferiority to active control (18) • Choice of an appropriate control is based on the current standard of care for the intended subject population • Extent of knowledge about the effect size of the active control
Placebo control (i.e. sham)	Control group uses or is exposed to another or same device that is externally indistinguishable from the active device but whose stimulation is believed to have no therapeutic effect	• It may be challenging to construct a placebo control that appears to function like the investigational device
Standard of care/No intervention	Control group uses the standard of care and is not exposed to any active or sham device	• Standard of care/best medical management can provide evidence about any incremental benefit or risk, although the control may vary across study centers • No-intervention control o May present a challenge in recruiting subjects or keeping subjects enrolled o Has built-in bias, because control group subjects expect to receive no benefit, whereas experimental group subjects expect to receive a benefit; an extension period can be offered where all subjects recruited in the study can utilize the trial device
Subjects act as their own control	Subject serves as concurrent control to self (e.g. split-face, where active stimulation is administered on one side of the head and sham stimulation to the other)	• Use of the subject as his/her own concurrent control allows for the advantageous use of the correlation within the subject • Only possible when the effect of the experimental device and control intervention are local and do not overlap
Non-concurrent — Not recommended		
Baseline control	Subject's outcomes at baseline compared with outcomes at endpoint evaluations	• Use of baseline outcomes as a comparison for outcome at the endpoint evaluations is inadequate for most therapeutic studies since subjects may improve for reasons unrelated to investigational device (e.g. regression to the mean, placebo effect)
Historical control (i.e. performance goal) — subject-level data on a parallel group	Control group consists of a different group of subjects treated in the past for whom individual subject-level data are available for the same outcomes and covariates as the current study	• A significant concern is comparability between the two groups with respect to baseline covariates • The use of a comparator study separated in time can introduce severe and unknown selection bias; however, statistical methods such as covariate analysis or propensity score analysis can potentially address some concerns • The historical control group may not reflect current practice of medicine and may include a different subject population and/or outcome than the contemporary study (temporal bias)

(continued)

Table 3. Continued.

Description	Comments
	• This control is challenging when subjective endpoints are used or when all of the necessary endpoints were not previously evaluated or evaluated in different ways • Presents a significant challenge in addressing the implications of missing data • Sensitivity and missing-data analyses may address some concerns associated with bias

Table 4. Recommendations for clinical trials of neuromodulation devices for the acute treatment of migraine in adults.

	Recommendations	Comments
Subject Selection		
Frequency of attacks	• Attacks of migraine should occur 2-8 times/month (1) • Subjects experiencing >8 attacks/month may be considered for inclusion in clinical trials specifically designed to evaluate the efficacy of the device in those with a high burden of disease	• In clinical trials of medications, a maximum frequency of 8 attacks/month is recommended to reduce the probability that those with incipient medication overuse, medication-overuse headache, or chronic migraine will be included in the trial (1); • Subjects in trial assessing noninvasive neuromodulation modalities, patients with a high burden (i.e. >8 attacks/month) may be considered for inclusion in clinical trials of neuromodulation devices due to the enhanced safety of devices
Trial Design		
Timing of administration	• The timing of acute treatment must be consistent with the objectives of the trial (1) • Both early treatment and treatment when migraine headache pain is of at least moderate intensity are acceptable, as long as this is pre-specified • Subjects should record the time and pain intensity at the time of treatment in the trial diary (1)	• Clinical trials of medications recommend that subjects wait until pain intensity is moderate or severe before treating to increase the specificity of migraine diagnoses and treatment effects (1) • With devices, earlier treatment may be considered due to enhanced flexibility and tolerability compared with drugs
Number of attacks treated/consistency of response	• The efficacy of the first treated attack is recommended for the assessment of the primary endpoints • If appropriate training is not possible, the second treated attack can be used for the assessment of the primary endpoints as long as appropriate blinding is maintained • Evaluation of the efficacy across multiple attacks (typically 5) is recommended for the evaluation of secondary endpoints	• In most clinical trials of medications for the acute treatment of migraine, the first treated attack is used in the evaluation of efficacy to minimize the placebo effect (1) • If the possibility of inappropriate use of the device is a concern, efficacy should be measured over a higher number of attacks for a more reliable evaluation
Rescue medication[a]	• The use of rescue medication should be allowed at any time after the first primary efficacy time point, typically 2 hours after the initial administration of treatment (1) • Use of rescue medication before the 2-hour endpoint should be considered a treatment failure unless an earlier time point for rescue was pre-specified in the trial protocol (1)	

(continued)

Table 4. Continued.

	Recommendations	Comments
Evaluation of Results		
Primary endpoint[a]	The percentage of subjects who are pain free at 2 hours after treatment, before the use of any rescue medication	• Pain freedom at 2 hours post-dose should be the primary endpoint in all clinical trials evaluating the efficacy of neuromodulation devices for the acute treatment of migraine
Co-primary endpoint[a]	Absence of the most bothersome migraine-associated symptom at 2 hours after treatment	• It is not mandatory to have a co-primary endpoint, but it is useful to consider this, as pain is not always the most bothersome symptom during migraine attacks • Recent findings suggest the opportunity to consider also cognitive dysfunction, in addition to the classic quartet of nausea, vomiting, sensitivity to light, and sensitivity to sound (19)
Secondary endpoints[a]	• The following endpoints are shared with clinical trials of medications: o Relapse o Sustained pain freedom o Total freedom from migraine o Headache intensity o Headache relief o Time to meaningful relief o Time to pain freedom o Duration of attacks o Use of rescue medication o Global evaluation o Global impact (functional disability and quality of life) o Effect on associated symptoms (nausea, vomiting, photophobia, phonophobia) o Time between onset of headache and delivery of treatment o Subject preference o Treatment of relapse • Use of acute medications or their improved efficacy • Device usability • Device use (number of stimulation and/or total duration of the stimulation)	• Refer to (1) for details on secondary endpoints shared with clinical trials of medications • Neurostimulation devices may contribute a reduction in the use of acute medications or improve their efficacy — an especially important outcome for subjects who are: o Overusing acute medications o At risk of becoming acute medication overusers

[a]Recommendations coincide with current recommendations for clinical trials of pharmaceuticals; for more information, refer to Diener et al. 2019 (1). For the measurement and reporting of adverse events please refer to Table 2.

Compared with medications, randomized controlled trials of devices are often more difficult, and outcomes depend heavily on the training and experience of investigators, clinical trial personnel, and subjects; these challenges can be exacerbated by product modifications, which are rare with medications but relatively frequent with devices (24). Health technology assessments can be performed by transnational agencies, but they are often delegated to national or local agencies that use different process and protocols (25,26). The IHS recently published an official position statement intended to facilitate and standardize the conduct of health technology assessments of medications and neuromodulation devices approved and/or cleared for the acute and preventive treatment of migraine (27).

11. Methods used for the development of these guidelines

These guidelines represent an activity of the Clinical Trials Committee of the IHS. The initial work was

Table 5. Recommendations for clinical trials of neuromodulation devices for the preventive treatment of migraine in adults.

	Recommendation(s)	Comments
Study Design		
Design types	With invasive devices, a post-double-blind, open-label period, where patients receiving placebo are rolled over to active stimulation, is highly recommended due to ethical reasons.	
Endpoints		
Primary[a]	Change from baseline in the number of migraine days over a pre-specified period of time (2,3)	Typically 12 or 24 weeks
Alternative primary[a]	• Change from baseline in the number of moderate/severe headache days over a pre-specified period of time • 50% responder rate for the reduction of migraine days over a pre-specified period of time (2,3)	
Secondary[a]	The following secondary endpoints are recommended (2,3): • Moderate/severe headache days[b] • Migraine days[b] • 50% responder rate for the reduction of migraine days (if not used as a primary endpoint) • Headache severity • Peak headache pain intensity • Cumulative hours per 28 days of moderate/severe pain • Onset of effect • Effect on the most bothersome symptom • Acute treatment utilization • Depression and anxiety • Patient global impression of change • Functional impairment scale • Migraine functional impact questionnaire • Migraine physical function impact diary (2,3)	In the case of clinical trials where the device is used for both acute and preventive treatment, the number of stimulations used for acute treatment should also be captured
Exploratory[a]	• Symptom-free days • Headache- and symptom-free days • Healthcare outcomes/Quality-of-life • Migraine-specific Quality-of-Life questionnaire • Headache Impact Test • Migraine Disability Assessment scale • EuroQoL-5 Dimension questionnaire • 36-Item Short Form Health Survey	Other tests or scales to asses some of these endpoints may be used provided that they have been validated for the purpose
Device-specific	• Device usability • Device use o Number of stimulations o Total duration of the stimulation	
Economic aspects[a]	• Assess reductions in work productivity and activity using the Work Productivity and Activity Impairment instrument or other validated tools (2,3) • Quantification of direct and indirect costs	Some devices can be quite expensive and they might not be subsidized by the local health systems nor covered by insurance. Thus, a more detailed evaluation of the economic impact seems useful.

[a]Recommendations coincide with current recommendations for clinical trials of pharmaceuticals; for more information, refer to Tassorelli et al., 2018 and Diener et al., 2020 (2, 3).

[b]If not used as the primary endpoint.

For the measurement and reporting of adverse events please refer to Table 2.

Table 6. Considerations for clinical trials of neuromodulation devices in children and adolescents.

	Recommendation(s)	Comments
General	Neuromodulation device can be tested in children and adolescents only after evidence on efficacy, tolerability, and safety has been obtained in adults.	This is particularly true for invasive devices and for devices that may alter cortical excitability.
Endpoints		
Primary[a]	Change from baseline in headache days or migraine days (4)	
Alternative primary[a]	• Change from baseline in moderate/severe headache days • 50% responder rate for the reduction of migraine days (4)	
Secondary[a]	• Headache-related characteristics • Headache hours/28 days • Depression and anxiety • Frequency of migraine aura • Pediatric Migraine Disability Assessment scale (4,20)	Validated scales should be used for the assessment of depression and anxiety
Exploratory	• Headache-free days • Symptom-free days • Biomarkers • Use of acute medications • Patient Global Impression of Change (4)	
Device-specific	• Device usability • Device use (number and/or total duration of stimulations)	
Economic considerations	Assessments of the economic value of preventive treatment for migraine should capture: • Direct costs — price of medical treatment • Indirect costs — lost time from school of the patients or from work of the parents (4)	Diaries or validated tools can be used for this purpose

[a]Recommendations coincide with current recommendations for clinical trials of pharmaceuticals; for more information, refer to Abu-Arafeh et al., 2019 (4).
For the measurement and reporting of adverse events please refer to Table 2.

performed by an international working group of experts on migraine and neuromodulation devices that was assisted by a small group of junior headache researchers. The process used to develop the guideline involved:

- Reaching consensus on a definition of neuromodulation device
- Evaluating the designs and endpoints of clinical trials conducted to test the efficacy of neuromodulation devices in the acute or preventive treatment of migraine in the past 20 years (Table e-1 and Table e-2 in the Supplementary Material)
- Preparing and revising multiple versions of the recommendations until all members of the working group could support them
- Soliciting and incorporating feedback on the expert analysis from:
  - Stakeholders that included pharmaceutical and neuromodulation device manufacturers and patient associations
  - IHS members, who had access via the IHS website
- Obtaining the final approval of the IHS Board of Trustees

Clinical Implications

- Neuromodulation devices are emergent in the migraine armamentarium, with several devices recently approved in the Europe and the United States for acute and/or preventive treatment
- The absence of a trial guideline that recognized the distinct approach to treatment of migraine used by neuromodulation devices limited understanding of their therapeutic potential
- These recommendations for the assessment of neuromodulation devices in the acute and preventive treatment of migraine will facilitate research and help to clarify their optimal role in clinical practice

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