Guidelines of the International Headache Society for Controlled Clinical Trials in Cluster Headache

v. 3.2

April 2022

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Suggested journal: Cephalalgia

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Content

Abstract

In 1995, a committee of the International Headache Society (IHS) developed and published the first edition of the *Guidelines for controlled trials of drugs in cluster headache.* These have not been revised. With the emergence of new medications, neuromodulation devices and trial designs, an updated version of the IHS *Guidelines for Controlled Clinical Trials in Cluster Headache* is warranted. Given the scarcity of evidence-based data for cluster headache therapies, the update is largely consensus-based, but takes into account lessons learned from recent trials and demands by patients. It is intended to apply to both drug and neuromodulation treatments, with specific proposals for the latter when needed. The primary objective is to propose a template for designing high quality state-of-the-art controlled clinical trials of acute and preventive treatments in episodic and chronic cluster headache. The recommendations should not be regarded as dogma and alternative solutions to particular methodological problems should be explored in the future and scientifically validated.

Abbreviations

AE: Adverse event; CH: Cluster headache; CCH: Chronic cluster headache; CHQ: the Cluster Headache Quality of life scale; CHS: the Cluster Headache Scales ECH: Episodic cluster headache; ICHD: International Classification of Headache Disorders; IHS: International Headache Society; ITT: Intention to treat; FAS: full analysis set; MOH: Medication-overuse headache; PROMs: Patient reported outcome measures; RCT: Randomised controlled trial; VAS: Visual Analog Scale; VRS: Verbal Rating Scale.

Introduction

Since the publication of the first Guidelines for Controlled Clinical Trials of Drugs in Migraine in 1991 (1), the Clinical Trials Committee of the International Headache Society (IHS) has been active in the development and publication of guidelines for controlled clinical trials of treatments for primary headache disorders. Recently, new and updated guidelines for "trials of acute treatment of migraine attacks in adults", "trials of preventive treatment in adults with episodic and chronic migraine", "trials of preventive treatment for children and adolescents with episodic migraine" and "trials with neuromodulation devices for the treatment of migraine" have been published (2–6). However, the guidelines for controlled clinical trials in cluster headache (CH) date from 1995 and were mainly focussing on drug trials (7). Over the past decade, promising new therapeutic options have emerged, including drugs, devices and nerve blocks, and recent clinical trials suggest that the 1995 guidelines need revision and updating (8–11). The new guidelines will therefore cover designs for pharmacological treatments and neuromodulation devices. Along with trial design, data collection methods have evolved as well (e.g. electronic diaries) and endpoints have changed. There is now a greater emphasis on patient-reported quality of life and cost-effectiveness of novel treatments, in line with the demands of regulatory bodies throughout the world that make decisions on reimbursement of new treatments. There is also an increasing demand of more direct involvement of patients in trial strategies favouring patient-centered designs. Using the lessons learned from recent trials and incorporating new approaches, these guidelines are designed to advance the quality of future CH trials and subsequently improve CH treatment. Finally, as CH is rare in children, the present guidelines will primarily focus on adults and adolescents (12 – 17 years old).

1. General recommendations for trial design

1.1 Design types

Recommendations:

a) For pivotal prevention studies, a parallel group, double-blind, placebo-controlled design is recommended.

b) Cross-over designs can be used in acute studies if the investigational treatment has no long term carry-over effect or side effects that may invalidate blinding.

c) Add-on preventive trials are acceptable, especially in populations of patients with high disease burden and a history of failures/intolerance/contraindications to other treatments who have a partial response to an ongoing treatment, of which the dose has been at stable for $\geq$ 2 weeks and will not change during the trial.

d) Double-blind trials evaluating both acute and preventive efficacy of a drug or a device may be considered only after the treatment has proven to be effective for both indications (ie. acute and preventive) individually in separate trials.

Comments:

a) In pivotal trials, the study should be multicentre and adequately powered to assess efficacy of an investigational treatment. Tolerability and safety (as determined by laboratory testing, physical exam, clinical adverse events, and other appropriate tests) must also be assessed.

In the future, alternative designs could be considered in order to minimise (or eliminate) the time patients are on placebo and in episodic CH (ECH) to minimise the risk of spontaneous early remission. Examples of alternative designs encompass, but are not limited to: randomised withdrawal design (enrichment-enrolment randomised withdrawal), adaptive randomisation design, early-escape design, optional switch design, non-inferiority/equivalence trial, randomised placebo phase design or retention trials. A separate publication describing advantages and limitations of these possible alternative study designs is being prepared by the subcommittee.

Open or single-arm studies are only advisable in early and long-term safety studies.

In trials on acute treatment, an active control, e.g. subcutaneous or nasal sumatriptan, or nasal zolmitriptan, can be included alongside placebo in a three-armed trial if required for health technology assessments.

Active comparators can be used in randomized controlled trials, as long as both the investigational therapy and the comparator have been proven superior to placebo in previous trials.

b) In cross-over trials, carry-over effects should be evaluated using appropriate statistical tests. Study design should aim, however, to avoid carry-over effects taking into account the PK /half lives of the investigational drug and defining appropriate washout periods.
Cross over designs can be problematic if patients become unblinded to the product during one period due to adverse effects. This may also create problems if patients that do not experience efficacy in the first period, or have an adverse event in one period do not want to cross over, thus reducing the power of the study.

d) Some neuromodulation devices and drugs might show both acute and preventive efficacy. This can be assessed in appropriate designs, once separate trials have demonstrated their efficacy respectively in the acute treament of CH attacks and for their prevention. As mentioned in the comment to a), novel designs should be conceived in the future also to assess acute and preventive effects in the same trial.

1.2 Blinding

Recommendations:

a) Trials on new treatments in CH should be conducted using a randomised double-blind design.
b) For most neuromodulation devices, blinding represents a significant challenge due to an active signal. Strategies to enhance and preserve blinding should be used whenever possible, including stimulation protocols that do not produce sensory stimulation and are thus not perceivable by the participant, or protocols that deliver perceptible but subtherapeutic stimulation in the sham arm if dose-response studies have established an effect threshold.
c) Successful blinding should be assessed at the end of the study for both patients and investigators involved in a trial (see blinding assessment).

Comments:

b) 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. Alternatively, a third unblinded investigator can be involved, but those trusted third parties should have no further interaction with participants to allow for investigators, assessors, and participants to remain blinded to treatment assignments throughout the study.
In device studies, crossover designs may be challenging because active treatments may cause sensations which will not occur or will occur less with placebo/sham treatments; participants will thus easily recognise the difference between active and placebo/sham.

When blinding the participants and/or investigator is complicated or not possible, the following measures are recommended:

1) A dose-response relation should be explored.
2) Independent third-party evaluators of clinical measurements and/or endpoints should be blinded to the intervention assignment (blinded assessor).
3) Participants naïve to the neuromodulation technique investigated should be prioritised.

In the informed consent form, participants should be instructed to refrain from consulting media with information related to the trial and from contact with other participants in the trial. Furthermore, it should be explained to participants that the perceptible stimulation-induced effects are not necessary to obtain the therapeutic benefit but are potentially stimulation-related effects.

1.3 Randomisation

Recommendation:

In pivotal studies, participants must be randomised 1:1.

1.4 Stratification

Recommendation:

When a decision is made to study important subgroups or strata (i.e., multiple centers, covariates or confounders considered highly predictive of participant outcomes [ECH vs chronic CH (CCH)], presence or absence of certain comorbidities, concomitant drug use) stratified randomisation, in which randomisation occurs separately in each of the pre-specified strata, should be considered.

Comments:

Randomisation alone cannot ensure that groups will be balanced for factors that could influence the treatment response, which is particularly true in studies with smaller or modest sample sizes.
As sample size increases, randomisation will increasingly ensure that treatment groups will be balanced for certain covariates or confounders. Only strata based on covariates that have historically demonstrated effect on the primary efficacy endpoint(s) should be included. To avoid too small sample sizes, stratification should be limited to as few strata as possible. If stratification at randomisation is not performed and if imbalances for important subgroups are observed, then adjustment for these covariates must be included in the data analysis plan.
Stratification variables may be different for preventive and acute trials.

1.5 Training for devices and non-oral medications

Recommendations:

a) Sponsors should ensure that investigators have or receive the appropriate amount of training and experience necessary for the safe and effective use of a device or non-oral drug administration. Training is likely to vary across, as well as within, sites, which may directly impact assessment. Standardised tutorials for investigators are therefore recommended.

b) In the case of auto-injections and self-use devices, participants should be appropriately trained by expert personnel and they should also be provided with instructions for use to review at home, such as online video tutorials and other training materials specific to auto-injectors or devices.

c) Invasive neuromodulation devices require appropriate and certified training for the operators. Surgical implantation techniques should be standardised across centers/surgeons, as far as possible; the initial procedures must be done with an experienced instructor.

Comments:

a) The safe and correct use of a device represents a specific requirement for most neuromodulation devices. The correct use of drugs via non-oral routes (e.g. inhalation, nasal spray, transcutaneous iontophoresis, subcutaneous auto-injection) also impacts on treatment efficacy and tolerability. Continued training may be needed as part of the clinical study plan to facilitate safe use of the device.

b) For self-administered injection or stimulation, device familiarity and user knowledge are important to properly test the efficacy of the injection/device and to minimise side-effects. Use of devices requires more patient interaction than a drug, which is why training is essential.
A human factors study evaluating ease of use of a device, for either a new neuromodulation or medication delivery system, is encouraged.

2. Selection of participants

2.1 Cluster headache definition

Recommendations:

a) Eligible patients should fulfil the diagnostic criteria for CH according to the most recent version of the International Classification of Headache Disorders (ICHD) of the IHS.

b) Patients fulfilling criteria for ECH or CCH should be assessed in separate trials for preventive treatments, and preferably also for acute treatments.

Comments:

a) Clinical trials for CH should include patients that meet the ICHD criteria to avoid population heterogeneity. Therefore, patients with other or additional trigeminal autonomic cephalalgias (12), should not be included in CH trials. Instead, they should be studied separately with adapted trial guidelines.

b) Although acute attacks of ECH and CCH are similar clinically, they can respond differently to both acute (13–15) and preventive treatment (8,9,16). Therefore, until these differences and their pathophysiological correlates are better understood, we recommend separate preventive trials for ECH and CCH patients, and preferably also separate acute trials. Alternatively, they could be included in the same trial, as long as they are stratified at randomisation (see 1.4) with separate power calculations for each subgroup.

2.2 Specific patient populations and attack characteristics

Recommendations:

In addition to separating ECH and CCH, subgroups may be defined based on clinical features and treatment refractoriness, the latter particularly for treatments that either are invasive or carry high levels of risk. The following patient/attack subtypes need special considerations:

a) CCH patients who have a persistent high attack frequency (e.g. ≥ 14 attacks per week on average) and cannot be managed with available preventive treatments should be characterised and *post hoc* subanalysed.

b) Patients with side shifts may be included, except in trials with unilateral neuromodulation.

c) Patients reporting mild persistent ipsilateral headache between attacks may be included, provided hemicrania continua is excluded based on the most recent ICHD criteria (Mamura et al 2010).

d) Adolescent (12 – 17 years old) patients and children should ideally be studied in separate trials.

e) Patients with a family history of CH may be included, but should be recorded.

f) Patients who satisfy ICHD criteria for CH but have atypical features (absence of cranial autonomic symptoms, post-traumatic onset, cluster-tic syndrome) should be excluded or studied separately to avoid introducing heterogeneity.

Comments:

a) At present, there is no consensus on the definitions of "medically refractory", "drug-resistant" or "medically intractable" CCH. Because of the lack of randomised controlled studies (RCTs) very few medications are approved for CH prevention, galacanezumab being the only one, at the time of writing, in the US for ECH. Nonetheless, in clinical practice and according to available guidelines (17,18), various drugs can be effective and prescribed "off-label". Patients with persistent high attack frequency who cannot be managed with these preventive drugs are considered to be most challenging to treat and should be *post hoc* analysed separately. They are the main target population for extracranial implantable neuromodulation devices, like occipital nerve or sphenopalatine ganglion stimulators (10,11,19–21). Only CCH patients who meet the above criteria and have also failed at least one extracranial implantable neuromodulation device, if available and appropriate, can be considered for trials of intracranial implantable neuromodulation methods like deep brain stimulation.

b) Side shifts of attacks of CH may occur in approximately 20% of patients (22–26). These patients may be included in trials, except in trials of unilateral neuromodulation as attacks of CH may shift to the non-treated side (27).

c) Patients can report persistent ipsilateral mild headache with or without autonomic symptoms (miosis, ptosis) between attacks; these patients may be included provided hemicrania continua is excluded with an appropriately dosed indomethacin test.

d) CH is rare in adolescents and children while its severity is similar to that of adults and available treatment options are very limited. It is therefore important to offer these patients access to novel treatment strategies, but also to allow for adapted clinical trial rules, as for orphan diseases. Because of the small numbers and the fact that, akin to migraine trials (Evers et al 2008), a high placebo response may be expected, it does not seem appropriate to study adolescents and children together with adults in the same CH trial. We recommend to start with an open label study on efficacy and tolerability of a new treatment that should be followed by a randomized controlled trial. The RCT designs should be adapted to this patients group: for instance, cross-over, head-to-head comparator or other alternative protocols can be considered.

2.3 Other primary headaches

Recommendations:

a) Patients with other ongoing concomitant infrequent primary headache types, such as episodic migraine or episodic tension-type headache, are allowed to participate in a trial, if they can clearly differentiate them from attacks of CH based on the quality of pain and associated symptoms.

b) Patients with concomitant chronic migraine or chronic tension-type headache should not be included.

Comments:

a) Tension-type headache and migraine are common, and it is not rare that they co-occur in CH patients. If chronic (fulfilling the ICDH criteria for chronic migraine or chronic tension-type headache), they may contribute significantly to disability and cause confusion in distinguishing the different headache types.

b) Subjects with a past history of chronic migraine or chronic tension-type headache can be included.

2.4 Secondary headaches

Recommendation:

Patients with secondary headaches should be excluded

Comments:

Medication-overuse headache (MOH) due to frequent use of analgesics is rare in patients with CH and occurs particularly in those with a personal or family history of migraine (28). On the other hand, many CH patients are using triptans as an attack treatment on a frequent or daily basis without developing MOH.

Subjects overusing simple or combination analgesics above the ICHD-defined monthly thresholds should not be included. However, frequent or daily triptan use for CH attack treatment is allowed, but should be recorded.

2.5 Frequency of attacks

Recommendations:

Episodic cluster headache:

a) ≥ 4 typical (treated or untreated) attacks per week for acute trials

b) ≥ 4 typical (treated or untreated) attacks per week for preventive trials.

Chronic cluster headache:

a) ≥ 4 typical (treated or untreated) attacks per week for acute trials.
b) Attack frequency of ≥ 4 attacks per week for ≥ 4 weeks before enrolment in preventive trials

Comments:

Attacks must fulfil the most recent version of the ICHD diagnostic criteria for CH attacks and should be documented in a daily real-time electronic diary with time-stamps.

ECH b) We recommend that patients have at least four attacks a week to ensure that ECH patients are in a full-blown bout. We also recommend, where useful, pre-screening as described in 2.6.

CCH b) The historic attack frequency should be stable for a minimum of 4 weeks in CCH preventive trials to minimise the risk of/avoid spontaneous changes in attack frequency during the study.

2.6 Duration of cluster headache and cluster headache bouts

Recommendations:

Episodic cluster headache:

a) Patients who have had ≥ 2 bouts previously.
b) Patients' usual bouts should last ≥ 4 weeks.

Chronic cluster headache:

Patients with ≥ 1-year duration of disease (see most recent ICHD criteria).

Comments:

a) Patients should not be included during their first bout.

b) In trials investigating the effect of acute treatments, patients with shorter bouts can be included.

In ECH prevention trials, the likelihood of spontaneous remission occurring prior to the measurement of the primary endpoint must be minimised. Patients should therefore, only be included when they are in the first half of their usual bout period.

Moreover, it may be useful to pre-screen ECH patients in remission so that they can enter a baseline observation period followed by randomisation and treatment as soon as a bout starts.

2.7 Age at entry in the trial

Recommendations:

a) For adult patients, an age range of 18-70 years is recommended.

b) For adolescent patients an age range of 12-17 years is recommended.

Comments:

a) Medical devices are not associated with drug-drug interactions. Non-invasive devices may thus be safely assessed in people older than 70 years. However, be aware that older patients often have comorbid diseases and concomitant therapies that might interact with the investigational device and impact the performance.

b) In adolescents, open label studies are allowed to collect efficacy and tolerability data allowing the subsequent design a randomized controlled trial. Alternative trial designs should be considered (see also 2.2). Data on safety and tolerance of a new treatment administered to children and adolescents should be carefully examined before enrolling them in a trial (5).

2.8 Sex

Recommendations:

a) Males and females with CH are eligible to participate in clinical trials.

b) Whenever possible, a pre-specified subanalysis is recommended to evaluate a possible sex difference in response.

Comments:

a) For female participants, the ovarian status should be specified and, in non-menopausal women, the menstrual period should be recorded in the e-diary; sex hormone treatments should also be monitored.

b) There may be sex-related differences in clinical phenotypes, potentially causing sex-related differences in outcome (29,30). The male-to-female ratio in CH has decreased from 5-7:1 in initial studies (31) to 2-3:1 in more recent surveys (32), which will likely be reflected in clinical trials.

2.9 Concomitant drug use

Recommendations:

a) In ECH preventive trials, ideally no other preventive therapy should be allowed.

b) In ECH acute trials, verapamil may be allowed, but the given dose must have remained stable for at least 2 weeks. It is, however, recommended to perform a pre-specified *post-hoc* subanalysis in such patients.
c) In preventive trials, use of acute medications should be allowed.
d) In acute trials, acute medications should be allowed during the baseline (run-in) period.
e) In CCH trials, preventive agents are allowed as long the doses have been stable for at least 2 weeks pre-enrolment and are not modified during the trial.
f) Illicit substance use is not allowed.
g) Treatment of concomitant conditions is allowed as long as the drug dose has been stable for at least 2 weeks and remains stable in the course of the study, and no significant drug-drug interaction is expected with the new treatment.
h) The following should not be allowed:
    i. Botulinum toxin injections or monoclonal antibodies targeting calcitonin gene-related peptide pathway in the past 3 months.
    ii. Suboccipital infiltrations with steroids and/or local anaesthetics, or use of oral steroids in the past month.
    iii. Other extracranial injection procedures

Comments:

a) In ECH preventive trials, allowance of a stable dose of verapamil may exceptionally be considered in patients not willing to discontinue the drug and provided that they still have a consistent attack frequency of ≥ 4 typical attacks per week. It is, however, recommended to perform a pre-specified post-hoc subanalysis in such patients.

b) In ECH acute trials, a stable dose of verapamil is allowed, but these patients should also be subanalyzed.

c) Repeated treatment with neuromodulation devices are not allowed for attack treatment in clinical preventive trials, because some of them could have a preventive effect which will bias the outcome of the preventive investigational therapy (10).

f) Drugs are defined as illicit if they are forbidden by law, rules or custom. Apart from cannabinoids, which are allowed in certain countries or states, illicit drugs will most often include *non-prescription* stimulants (e.g. cocaine, methamphetamine, amphetamine, 3,4-metylénedioxsymethamphetamine (MDMA)), *non-prescription* central nervous system depressants (e.g. gamma-hydroxybutyrate (GHB), heroin, barbiturates,

benzoiazepines, flunitrazepam) and hallucinogens (e.g. psilocybin, ketamine, lysergic acid diethylamide (LSD)).

Regular use of cannabinoids is significantly more prevalent in CH patients, in particular males, than in the general population (33). Such patients, if they are not willing to refrain from cannabinoid use during the trial, can be considered for inclusion depending on the context of the trial. The type and frequency of cannabinoid use should be documented and these patients should be be *post hoc* subanalyzed. All other illicit drugs are not allowed.

g) Allowance of treatments for concomitant diseases can be less stringent in device trials, as there are no off-target side effects.

h) In a trial design comparing or adding a new treatment to "usual care" (see below), suboccipital infiltrations or oral corticosteroids may be considered part of "usual care".

2.10 Concomitant disorders

Recommendations:

a) Patients with severely disabling concomitant disorders that may influence the conduct of a trial or the interpretation of its results, or be negatively impacted by the new treatment should be excluded.
b) Patients with major depressive and/or generalized anxiety disorders, as defined by Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria (34) should not be included.
c) Patients suffering from a substance use disorder, as defined by DSM criteria (34), should be excluded.
d) Patients with concomitant disorders requiring regular monitoring by MRI should not be included in trials using implantable non MR-compatible devices.

Comments:

b) Anxiety and/or depressive mood are frequent in CCH patients (35,36). Suicidal ideation is also reported in CCH during and between attacks, and in ECH during attacks or bouts (37). Patients with these features can be included, if their symptoms are mild and their mental status is monitored during the trial.

2.11 Exclusions

Recommendations:

The following groups are excluded:

a) Patients who are allergic to compounds similar to the study medication or to excipients contained in the study formulation.
b) Female patients who are pregnant or do not use adequate contraceptive methods or are breastfeeding.

Comments

Depending on the investigational drug, it may be considered to exclude male patients who do not agree to use a reliable birth control method.

2.12 Participation in multiple trials

Recommendations:

Patients may not participate simultaneously in different clinical trials; a trial extension (e.g., open-label phase of long-term safety) should be counted as part of a single trial.

Patients may participate simultaneously in a RCT and in a prospective registry, provided that the inclusion/exclusion criteria of the trial are satisfied.

A study centre should avoid conducting more than one trial at the same time with the same indication and the same inclusion/exclusion criteria. In case multiple trials with the same indication and inclusion/exclusion criteria are simultaneously conducted, patients should be randomly allocated to the different trials.

3. Specific recommendations for attack treatment trials in episodic and chronic cluster headache

3.1 General considerations

In attack treatment trials one should be aware that the pain is not always stable. Pain severity typically reaches a peak intensity within a few minutes and in the vast majority attacks will spontaneously resolve within 30 to 120 minutes (38). Atypical patterns of evolution may pose problems regarding the timing of administration of medication (either early or when the attack is fully developed), and in evaluation of results. Furthermore, it is important to note that preventive therapy may decrease intensity of pain as well as frequency of attacks (39).

3.2 Duration of baseline period

Recommendation:

A prospective baseline period of at least 1 week to verify the required frequency of attacks is recommended.

Comments:

The baseline period may be shorter or not needed, if participants have filled out a prospective attack diary that captures all the necessary variables before start of the study period, but a prospective baseline period should be preferred.

3.3 Timing of treatment

Recommendation:

The treatment should be given as early as possible in the attack, but only after the pain has reached at least a moderate intensity (2 on a 5-point scale: 0=no headache, 1=mild headache, 2=moderate headache, 3=severe headache and 4=very severe headache).

Comments:

The need for early treatment is evident, since CH attack onset can be rapid. However, it is recommended to wait until the pain reaches at least a moderate [2] intensity to ascertain a 'full-blown' attack is treated and to ensure that improvement of at least two points on the pain scale can occur.

3.4 Number of treated attacks

Recommendations:

a) In the double-blind phase of the trial, 1 to 5 attacks should be treated, but the primary analysis should always be on the first attack treated per person to avoid bias due to interindividual variability in the number of attacks treated.

b) An open label extension of 1-2 months should follow the double-blind phase in both CCH and ECH acute trials.

Comments:

a) It is recommended to treat more than one attack to evaluate response consistency. However, the half-life of the investigated drug, and thereby the potential carry-over effect, should be taken into consideration when planning the number of treated attacks. Since CH attacks occur frequently, treatment of multiple attacks will not prolong the trial.

A secondary analysis of multiple treated attacks and individual variability in number of treated attacks can be performed using proper statistical analyses.

b) for regulatory purposes, a 1-year follow-up and a minimal number of attacks treated per month may be required.

3.5 Rescue therapy for acute attacks

Recommendation:

Rescue therapy must always be provided, but should not be allowed before 15 minutes following the administration of the treatment under investigation.

Comments:

For ethical reasons, participants must be allowed to use rescue therapy, but an adequate minimum interval (usually at least 15 minutes) following the investigational treatment is required.

3.6 Outcome measures

3.6.1 Attack report form

Recommendations:

a) A headache diary (paper or preferably electronic) should be used for recording attacks and their characteristics
b) Additional information on attack characteristics could be recorded on a report form by an observer.
c) For evaluation of recommended primary and secondary endpoints recording of the following variables are recommended:
    a. Onset of attack
    b. Timing of rescue therapy if needed
    c. Severity of headache (see 3.6.2)
        i. Before administration of study drug or onset of device treatment
        ii. Before rescue treatment
        iii. At frequent intervals throughout the period during which the effect of treatment is expected or for at least 3 hours

Comments:

Headache-related variables and use of acute treatments are best captured with electronic diaries with time stamps, which allow capturing relevant time-specfic outcomes relative to onset of attack. E-diaries should be validated before using in clinical trials.

If e-diaries are not available, paper diaries and a stop-watch can be used to capture time-specific outcomes.

Other recommended secondary outcomes (time to normal functioning, time to next attack, patient global impression of change, patient preference in cross-over trials on a validated scale) should also be recorded.

3.6.2 Severity of headache

Recommendations:

Recording of pain severity is recommended using a five-point ordinal scale: 0=no headache, 1=mild headache, 2=moderate headache, 3=severe headache and 4=very severe headache.

Comment:

Alternatively a 100-mm visual analogue scale (VAS) or an 11-point numerical rating scale (NRS) can be used.

3.6.3 Time to meaningful relief and responder rates

Recommendations:

Time to meaningful relief and 50% responder rates can be used as secondary outcome measures in acute CH trials.

Comments:

Since attacks of cluster headache are of short duration, time to effect provides a critical expression of efficacy. Time to meaningful relief is most often assessed using electronic diaries with time-stamp capabilities, which have largely replaced the use of stopwatches. The time-stamped information provides data about treatment response over a clinically relevant period of time instead of at pre-specified time points and allows diary entries to be analysed by powerful statistical methods such as survival analysis. Participants should note the time of onset of the attack and note when they experience meaningful relief. In acute treatment trials where participants treat multiple attacks, a 50% responder rate is defined as the proportion of participants who are pain-free after 15 min in at least 50% of treated attacks; it is an indication of effect consistency.

3.6.4 Rescue medications

Recommendations:

The proportion of attacks that require rescue therapy should be recorded.

Comments:

As rescue therapy (see 3.5), participants can use their usual attack treatment or a treatment optimized by the investigator, as long these treatments do not have risky interactions with the investigational treatment.

3.6.5 Patient reported outcome measures

Recommendations:

Patient reported outcome measures (PROMs) should be recorded. Use of validated and CH-specific tools is recommended.

Comments:

No standardized PROM's for CH have been developed yet. PROMs, not specific for CH, may include (40): the Patient Global Impression of Change scale (PGIC) as a measure of patient satisfaction (41); the Functional Impairment Scale (FIS) (42), a four-point scale that addresses functional status and intensity of impairment during daily activities; the EuroQoL- 5 Dimension Questionnaire (EQ-5D), a self-administered standardized measure of health status (43) (registration is needed to use this instrument) and the Work Productivity and Activity Impairment Instrument (44).

Quality of life scales specifically designed for CH patients are recommended. The Cluster Headache Quality of life scale (CHQ) comprises 28-items, grouped into four subscales labelled "restriction of activities of daily living", "impact on mood and interpersonal relationships", "pain and anxiety", and "lack of vitality" (45). The Cluster Headache Scales (CHS) has 36 items grouped into 8 subscales: "fear of attacks", "disability", "coping", "auto)aggression", "physical activity", "medical care", "medication side effects" and "financial burden" (46). The three latter items are not part of the CHQ that by contrast more explicitly addresses impairment in interpersonal relationships. Both CHQ and CHS are self-administered scales, but CHQ inquires about frequency of a disability or complaint (from "never" to "always") while CHS asks about the level of agreement with a statement (from "strongly disagree" to "strongly agree". Both scales are thus in part complimentary.

3.7 Primary endpoint

Recommendations:

Pain-freedom at 15 minutes without recurrence of any level of pain within 3 hours in the 1st treated attack.

Comments:

If attack freedom is reached within the pre-specified time frame but the attack recurs within 3 hours, this suggests inadequate therapeutic efficacy and thus should be considered a treatment failure.

Recurrence of pain after 3 hours of reolution should be considered a new attack.

3.8 Secondary endpoints

Recommendations:

A. Core secondary endpoints:
    a. Time to meaningful relief
    b. Sustained pain freedom without recurrence in all treated attacks
    c. 50% responder rate
    d. Pain relief at 15 minutes
    e. Sustained pain relief response after 15 minutes without worsening or use of rescue medication within 3 hours

B. Additional secondary endpoints:
    a. Pain-freedom at 5 and 10 min in the first treated attack or all treated attacks
    b. Pain relief at 5 and 10 min in the first treated attack or all treated attacks
    c. Percentage of attacks with need for rescue therapy
    d. Number of attacks per day during the study period
    e. Time to next attack
    f. Time to normal functioning
    g. Patient global impression of change (see 3.6.5 Patient reported outcome measures)
    h. Patient preference in cross-over trials (on a validated scale)

Comments:

b) If pain-freedom in all treated attacks is used as the primary endpoint, statistical analyses should be adjusted for non-independence.

d) Pain relief is defined as a ≥ 2-point change on the 5-point severity scale (from 4 to 2 or 1, from 3 to 1). Pain relief cannot be assessed for attacks of moderate severity (2 on the severity scale).

4. Specific recommendations for preventive trials

4.1 Outcome measures

4.1.1 Headache diary

Recommendation:

An easy-to-use validated electronic diary capturing pre-defined endpoints should be used preferentially.

Comments:

Headache related variables and use of acute medications are best captured with electronic diaries.

If e-diaries are not available, paper diaries are acceptable.

4.1.2 Headache severity

Recommendation:

Intensity of CH attacks should be recorded on a five-point ordinal scale: 0=no headache, 1=mild headache, 2=moderate headache, 3=severe headache and 4=very severe headache.

Comments:

Alternatively, a 100 mm visual analogue pain scale (VAS) or an 11-point numerical response scale (NRS) may be used.

Headache severity alone is not recommended as a primary outcome measure in preventive treatment trials, but may be included as a secondary endpoint for assessment of headache related disability.

4.1.3 Responder rates

Recommendations:

a) A 50% responder rate is defined as the proportion of participants achieving at least a 50% reduction from baseline in the number of CH attacks over a pre-specified period of time.
b) A 30% responder rate is defined as the proportion of participants achieving at least a 30% reduction from baseline in number of CH attacks over a pre-specified period of time.

4.1.4 Acute medications

Recommendation:

In preventive treatment trials the number and type of acute treatments should be recorded.

Comments:

In preventive treatments trials, efficacy of acute treatment may be included as an additional secondary endpoint.

4.1.5 Depression, anxiety and suicidal ideation

Recommendation:

Validated scales for depression, anxiety and suicidal ideation should be used in preventive treatment trials at baseline, at randomisation, at the end of the double-blind treatment period and at regular intervals throughout the study.

Comments:

Depression and anxiety contribute significantly to the burden of CH (35,36) (see 2.10). Validated scales for depression include Beck's Depression Inventory (BDI) (45), Patient Health Questionnaire-9 (PHQ-9) (46) and the Hospital Anxiety and Depression Scale (HADS) (47). For assessment of anxiety the State-Trait Anxiety Inventory (STA-I) (48), the Generalized Anxiety Disorder measure (GAD-7) (49) or HADS may be utilised. For assessment of suicidal ideation the Colombia-Suicide Severity Rating Scale (C-SSRS) (50) should be used.

4.1.6 Patient reported outcome measures

Recommendation:

Patient reported outcome measures (PROMs) should be recorded in preventive treatment trials. Use of validated tools, whenever available, is recommended.

Comments:

No standardized PROM's for CH have been developed yet. General patient recorded outcome measures (PROMs) do exist (40), but CH-specific Quality of Life scales, such as CHQ (45) and CHS (46) should be preferred (see 3.6.5).

Participant preferences can only be reliably measured in cross-over trials. It is important, however, to evaluate the wellbeing of study participants, and it is useful to define clinically meaningful changes. Whether participants would recommend the treatment to others, is considered not to be a useful outcome measure.

4.2 Episodic cluster headache

4.2.1 Duration of baseline period

Recommendation:

A prospective baseline period of ≥ 1 week is recommended.

Comments:

The baseline period may be shorter or not needed if participants have filled out a prospective attack diary that captures all the necessary variables before the start of the study period.

The onset of the bout in ECH must be recorded.

Due to the natural disease course of ECH, the attack frequency may decrease at the end of a bout and bout duration is highly variable (51). The baseline period should take this into account. It should thus not be too long and its upper limit could be adapted to the usual bout duration in individual patients.

4.2.2 Duration of treatment periods

Recommendation:

A double-blind phase of ≥ 3 weeks is recommended.

Comments:

The treatment period should reflect both the time required to optimise dose and the interval required for treatment effects to occur. Because the efficacy of some therapies develops gradually (i.e., may need weeks before becoming fully effective), a predefined period for assessing treatment effects should be selected based on available data.

The double-blind phase could be ended as soon as a study participant is free of attacks for at least one week.

Spontaneous remissions during the treatment period are possible due to the natural disease course of ECH. In patients with bouts lasting two months or more, or in patients with frequent bouts, an open-label extension phase may be considered to examine long term effects and prevention of subsequent bouts.

4.2.3 Primary endpoint

Recommendations:

When using a classical trial design, the primary endpoint should be the change from baseline in the number of weekly attacks for the entire double-blind phase.

Comments:

For short-term (or “transitional”) preventive treatments, the primary endpoint could be the change from baseline in attack frequency during a predefined post-treatment week depending on the expected effect onset and duration.

If an alternative trial design is chosen, the primary endpoint should reflect this accordingly.

If the double-blind phase was ended after an attack-free period of one week (end of bout), the primary endpoint should be the change from baseline in the number of weekly attacks for the double-blind period until the end of the bout.

4.2.4 Secondary endpoints

Recommendations:

A. Core secondary endpoints:
    a. 50% responder rate for the number of weekly attacks over the entire double-blind phase compared to baseline
    b. Proportion of participants with a ≥ 50% reduction in number of weekly attacks in each week of the double-blind phase
    c. Time to sustained attack freedom for ≥ 2 months, i.e. end of usual bout
    d. Change from baseline in mean intensity of attacks over the entire double-blind phase
B. Additional secondary endpoints:
    a. Change from baseline in the number of total attacks in each week of the DBP
    b. Change from baseline in the number of weekly severe attacks (pain rated as 3 or 4) over the entire double-blind phase
    c. 30% responder rate for the number of weekly attacks over the entire double-blind phase compared to baseline
    d. Change from baseline in mean weekly number of acute treatments over the entire double-blind phase
    e. Change from baseline in mean number of attacks with pain freedom at 15 min. after acute treatment over the entire double-blind phase
    f. Change from baseline in the presence and intensity of interval unilateral headache over the entire double-blind phase
    g. Specific patient-reported outcome measures (PROMs)
    h. Depression
    i. Anxiety
    j. Suicidal ideation

Comments:

In the case of an open-label extension phase, an additional secondary endpoint can be 'prevention of subsequent bouts' and, in patients at risk for chronification, 'prevention of progression to chronic CH'.

4.3 Chronic cluster headache

4.3.1 Duration of baseline phase

Recommendations:

A prospective baseline period of ≥ 2 weeks is recommended.

Comments:

The baseline period may be shorter if participants have filled out a prospective attack diary before start of the study period and have a stable weekly attack frequency since ≥ 4 weeks (see 2.5).
The weekly attack frequency in chronic CH may fluctuate. Cluster headache patients may have flare-ups; 35% of them report a degree of annual rhythmicity with worsening in the winter or spring months (52,53,54).

4.3.2 Duration of treatment periods

Recommendation:

A double-blind phase of 1-3 months is recommended.

Comments:

The double-blind phase may be modified according to the expected timing of the onset of effect. I.e., if the study treatment is expected to be fast acting, the double-blind phase could be shorter compared to a slow acting treatment. However, the double-blind phase should not be too short because of the known fluctuations in weekly attack frequency in CCH.

An open-label extension phase of 6-12 months after the double-blind phase should be considered. This will provide important information on safety, persistence and consistency of efficacy, long-term impact on the use of acute therapies, and usability in case of self-administered devices.

4.3.3 Primary endpoint

Recommendation:

For classical trial designs, the recommended primary endpoint is the change from baseline in the number of monthly attacks for the entire double-blind phase or for pre-specified periods within the double-blind phase (e.g. the last 4 weeks of treatment).

Comments:

If efficacy of the study treatment is expected to occur only after some delay, the primary endpoint should reflect this. The baseline period should then be compared to the last 4 weeks of the double-blind phase.
If the study treatment is expected to act rapidly, weekly attack frequency should be compared to baseline.

If an alternative trial design is chosen, the primary endpoint should be adapted accordingly.

4.3.4 Secondary endpoints

Recommendations:

A. Core secondary endpoints:
    a. 50% responder rate for the number of monthly attacks over the entire double-blind phase compared to baseline or a pre-specified period within the double blind phase
    b. Change from baseline in the mean intensity of attacks over the entire double-blind phase or a pre-specified period within the double blind phase
    c. Change from baseline in number of acute treatments over the entire double-blind phase or a pre-specified period within the double blind phase
    d. Time to onset of ≥ 50% reduction in monthly attack frequency compared to baseline
    e. Time to sustained attack freedom for ≥ 2 months, i.e. end of bout
B. Additional secondary endpoints:
    a. Change from baseline in the number of monthly severe attacks (pain rated as 3 or 4) over the entire double-blind phase or a pre-specified period within the double blind phase
    b. 30% responder rate for the number of monthly attacks over the entire double-blind phase or a pre-specified period within the double blind phase compared to baseline
    c. Change in efficacy of acute treatments (i.e., pain-freedom after 15 minutes) over the entire double-blind phase or a pre-specified period within the double blind phase
    d. Change from baseline in presence and intensity of interval unilateral headache over the entire double-blind phase or a pre-specified period within the double blind phase
    e. Specific patient-reported outcome measures (PROMs)
    f. Anxiety
    g. Depression
    h. Suicidal ideation

Comments:

If efficacy of the study treatment is expected to occur only after some delay, the secondary endpoints should reflect this. The baseline period should then be compared to the last 4 weeks of the double-blind phase.

If the study treatment is expected to act rapidly, secondary endpoints should be compared to baseline on a weekly basis.

Attack duration is higly dependent on the timing and speed of action of the acute treatment. Change in attack duration is therefore not recommended as an endpoint, but it is in part reflected in "change in efficacy of acute treatments" since efficacy is defined as pain-freedom after 15 minutes.

During the open-label extension phase, an additional secondary endpoint can be reversal from chronic to episodic CH.

5. Blinding assessment

Recommendation:

Because blinding can be challenging (see 1.2), it is important to assess how successful blinding was in the trial both for patients and study personnel.

Comments:

The quality of blinding can be assessed using questionnaires; indexes are available for the analysis of results (55).

6. Adverse events

Recommendations:

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.
b) 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 interview.
c) AEs should be reported separately for active treatment and placebo.
d) Any adverse event requiring hospitalisation should be recorded as a serious adverse event.
e) For implanted devices a long-term follow-up (≥ 1 year) is recommended.
f) For implanted neuromodulation devices, device- and surgery-related AEs should be distinguished from those related to the stimulation.

Comments:

e) Previous clinical experience with invasive neuromodulation suggests the importance of monitoring implanted participants over a long period.

7. Statistics and data-analysis

Recommendations:

The following should be prospectively defined in a pre-planned analysis of the data:

a) Primary, secondary, and exploratory endpoints
b) Modalities of data collection
c) The statistical analysis plans
d) Multiple-testing procedure
e) Sample size needed for statistical significance (power analysis)
f) Analysis populations
g) Rules for imputation of missing data
h) Methods for comparing the baseline and treatment phases and treatment groups

Randomised controlled CH trials should follow the principle of intention-to-treat (ITT), whenever possible.

Comments:

a),b) For efficacy endpoints, groups should be analysed according to randomisation assignment regardless of actual treatment received: full analysis set (FAS) using the ITT principle ("analysed as randomised"). A modified ITT (mITT) analysis including all randomized participants who received adequate treatment can be used in addition. For safety endpoints, it will be more reasonable to analyse participants according to treatment actually received ("analysed as treated").

c) The statistical analysis plan should include an alternative analysis plan if distribution of data does not meet assumptions of initial planned analyses.

f) Any exclusions of randomized subjects, including observations, from the full analysis set (FAS) should be fully justified. Studies should attempt to align with the ITT principle.

g) Methods for handling missing data must be described, such as multiple imputation methods. Last value-carried-forward is no longer the recommended method.

8. Trial registration

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

9. Publication of results

Recommendations:

a) All results, including primary, secondary endpoint and all safety data, either positive or negative, should be published.
b) Before initiation of the trial, the following is recommended:
    a. A publication committee should be formed addressing:
        i. Authorships based on the recommendations of the international Committee of Journal Editors (55).
        ii. Timeline for publication
    b. An independent safety monitoring board is recommended
c) At the time of trial initiation or at the end of recruitment a design paper with baseline data may be published.
d) Investigators should avoid entering into agreements with sponsors that restricts access to study data, limits analyses and interpretation, or interfere with the independent preparation and publication of manuscripts.

10. Steering committee

Recommendation:

In phase 3 trials, a steering committee comprised of academics, statisticians and company representatives is recommended.

A steering committee is not considered necessary in investigator-initiated trials.

11. Independent data safety and monitoring board

Recommendation:

An independent data and safety monitoring board and predefined stopping rule for futility or safety are recommended.

12. Post-approval registries

The IHS recommends that post-approval product registries (i.e prospective open-label observational studies) be initiated to evaluate the continued safety, tolerability and efficacy of newly approved treatments. These studies may furthermore provide data on compliance and adherence to new treatments. These registries may include patients with relevant comorbidities who were excluded from the original controlled trials. Whenever possible, post-approval registries and studies should use the endpoints recommended in the present guidelines.

13. Methodology used for development of these guidelines

In the development of this guideline, the previous guidelines have been thoroughly reviewed and all previous recommendations have been discussed by the committee. Furthermore, The *Guidelines for controlled trials in cluster headache* incorporates data and lessons learned from clinical trials that have been conducted since the latest guideline was published.

The present guidelines were first drafted by the chairs of the subcommittee and the writing committee and then revised several times by the other members of the *ad hoc* subcommittee and members of the IHS Standing committee until an agreement was reached and the pre-final version was supported by all. This version was submitted to various stakeholders including pharmaceutical and devices manufacturers as well as patient associations soliciting and incorporating their feedback on the expert analysis. Input was thereafter solicited from IHS members on the IHS website before final approval of the document by the IHS Board of Trustees.

The main purpose of these guidelines is to draw the investigator's attention to the problems inherent in drug trials in CH and to stimulate them to tackle these problems during the design phase of the trial. Recommendations are based on the clinical experience and research experience of the committee members. The recommendations should not be regarded as dogma and alternative solutions to particular methodological problems could be equally appropriate. For this reason, the guideline committee has decided to publish a separate article on potential alternative trial designs in CH.

Acknowledgements

Declaration of conflicting interest

The authors declare the following potential conflicts of interest with respect to authorship and/or publication of this article:

JS has received honoraria for contribution to advisory boards or oral presentations from Man & Science, Cefaly Technology, Lundbeck, Teva, Novartis and the Federal Public Service-Finances of Belgium; he was principal investigator in clinical trials sponsored by Novartis, Teva and Eli Lilly .

AHS has been a sub-investigator for clinical trials sponsored by Eli Lilly and Lundbeck.

RB reports no conflicts of interest.

RF received advisory honoraria from TEVA. Lilly and Lundbeck, and lecture fees from Novartis.

DW reports no conflicts of interest.

CSC reports no conflicts of interest.

HCD has received honoraria for contribution to advisory boards or oral presentations from: Ipsen, Lilly, Lundbeck, Novartis, Pfizer and Teva. The German Research Council (DFG), the German Ministry of Education and Research (BMBF) and the European Union support his headache research. HCD serves on the editorial boards of Cephalalgia and Lancet Neurology.

DF is consultant for Medtronic, Abbott, Boston Scientific and received research grants from Medtronic and Abbott.

DWD reports the following conflicts within the past 12 months: Consulting: Amgen, Atria, Cerecin, Cooltech, Ctrl M, Allergan, Biohaven, GSK, Lundbeck, Eli Lilly, Novartis, Impel, Satsuma, Theranica, WL Gore, Nocira, Perfood, Praxis, AYYA Biosciences, Revance. Honoraria: Vector psychometric Group, Clinical Care Solutions, CME Outfitters, Curry Rockefeller Group, DeepBench, Global Access Meetings, KLJ Associates, Academy for Continued Healthcare Learning, Majallin LLC, Medlogix Communications, MJH Lifesciences, Miller Medical Communications, WebMD Health/Medscape, Wolters Kluwer, Oxford University Press, Cambridge University Press. Research Support: Department of Defense, National Institutes of Health, Henry Jackson Foundation, Sperling Foundation, American Migraine Foundation, Patient Centered Outcomes Research Institute (PCORI). Stock Options/Shareholder/Patents/Board of Directors: Ctrl M (options), Aural analytics (options), ExSano (options), Palion (options), Healint (Options), Theranica (Options), Second Opinion/Mobile Health (Options), Epien (Options/Board), Nocira (options), Matterhorn (Shares/Board), Ontologics (Shares/Board), King-Devick Technologies (Options/Board), Precon Health (Options/Board), AYYA Biosciences (Options), Atria Health. Patent 17189376.1-1466:vTitle: Botulinum Toxin Dosage Regimen for Chronic Migraine Prophylaxis

PJG reports, over the last 36 months, grants, and personal fees or honoraria for serving on advisory board from Amgen and Eli-Lilly and Company, grant from Celgene, and personal fees from Abbott, AbbVie, Beckley Psytech, electroCore, Eli LillyAeon Biopharma, Allergan, Biohaven Pharmaceuticals Inc., Clexio, Electrocore LLC, eNeura, Epalex, GlaxoSmithKline, Impel Neuropharma, Lundbeck, Medtronic, Novartis, SalviaMundiPharma, Novartis, Pfizer, Praxis, Sanofi, Santara Therapeutics, Satsuma, Teva Pharmaceuticals, Trigemina Inc., and personal fees for advice through Gerson Lehrman Group and TEVA. In addition, MSM

has Guidepoint, fees for educational materials from Massachusetts Medical Society, Medery, Medlink, PrimeEd, UptoDate, WebMD, and publishing royalties from Oxford University Press, and Wolters Kluwer, and for medicolegal advice in headache, and a patent WO2018051103A1 issued magnetic stimulation for headache (No. WO2016090333 A1) assigned to eNeura without fee.

MM is chair of the medical advisory board of the CSF Leak Association; has served on advisory boards for Allergan, Autonomic Technologies Inc, Eli Lilly, Novartis, Pfizer, Salvia and TEVA; has received payment for educational presentations from Allergan, electroCore, Eli Lilly, Novartis and TEVA; has received grants from Abbott, Medtronic and electroCore; and has a patent on system and method for diagnosing and treating headaches (WO2018051103A1, issued).

AM is chief editor of Cephalalgia.

JSM is an employee of Vector Psychometric Group, LLC and has received honoraria/payment/reimbursement from the journal Cephalalgia (biostatistics editor). JSM has also received research grants/support from Amgen, Inc. and the National Headache Foundation.

ST received grants for research (no personal compensation): Allergan/Abbvie, Amgen, Eli Lilly, Lundbeck, Neurolief, Novartis, Satsuma, Zosano. Has served as Consultant and/or Advisor (honoraria) for Aeon, Allergan/Abbvie, Alphasights, Amgen, Aruene, Atheneum, Axsome Therapeutics, Becker Pharmaceutical Consulting, ClearView Healthcare Partners, CoolTech, CRG, Currax, Decision Resources, Defined Health, DRG, Eli Lilly, ExpertConnect, FCB Health, Fenix, GLG, Guidepoint Global, Health Science Communications, HMP Communications, Impel, InteractiveForums, Krog and Partners, Lundbeck, M3 Global Research, MJH Holdings, Neurolief, Novartis, Pain Insights, Inc, Palion Medical, Pulmatrix, Putnam Associates, SAI MedPartners, Satsuma, Spherix Global Insights, Strategy Inc, System Analytic, Taylor and Francis, Teva, Theranica, Trinity Partners, Unity HA, XOC, Zosano

RHJ has received honoraria for oral presentations from Lectures for Pfizer, Eli-Lilly, ATI, Merck, TEVA, Novartis, Lundbeck and Allergan. She is investigator in clinical trials with ATI, Eli-Lilly, Novartis and Lundbeck and Director of Danish Headache Center, Lifting The Global Burden of Headache and Founder of Master of Headache Disorders at University of Copenhagen Recived research funding from University of Copenhagen, Rigshospitalet, ATI, Lundbeck Foundation, The Medical Society in Copenhagen, NovoNordisk Foundation and Tryg Foundation.

MDF reports no conflicts of interest.

Funding

None

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