Guidelines of the International Headache Society for Controlled Trials of Preventive Treatment of Chronic Migraine in Adults

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This is the peer reviewed version of the following article: Guidelines of the International Headache Society for Controlled Trials of Preventive Treatment of

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Abstract

Quality clinical trials form an essential part of the evidence base for the treatment of headache disorders. In 1991, the International Headache Society Clinical Trials Standing Committee developed and published the first edition of the *Guidelines for Controlled Trials of Drugs in Migraine*. In 2008, the Committee published the first specific guidelines on chronic migraine. Subsequent advances in drug, device, and biologicals development, as well as novel trial designs, have created a need for a revision of the chronic migraine guidelines. The present update is intended to optimize the design of controlled trials of preventive treatment of chronic migraine in adults, and its recommendations do not apply to trials in children or adolescents.

Keywords

Chronic migraine, clinical trials, headache, drugs, preventive treatment

Introduction

Since 1991, the International Headache Society (IHS) and its Clinical Trials Standing Committee have been active in the development and publication of multiple guidelines for controlled trials of treatments for primary headache disorders (1-5). In 2008, the Committee developed and published the first edition of the *Guidelines for controlled trials of prophylactic treatment of chronic migraine in adults* (6). Since the first edition became available, several dozens of controlled trials of drugs, biologicals, and devices for the prevention of chronic migraine have been published (Appendix 1). Lessons learned from these studies have created a need to revise and update the existing guidelines to improve consistency and reliability in study design, patient population selection, outcome measures, and data analysis.

The present revision of the Guidelines focuses on drugs and biologicals. This guideline contains recommendations intended to assist in the design of well-controlled clinical trials of chronic migraine in adults, and they do not apply to studies in children or adolescents. A companion publication will focus on devices for the prevention of episodic and chronic migraine. For discussion of issues applying to clinical trials in general, the reader should refer to the Guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH, http://www.ich.org/products/guidelines.html) and consult general works on clinical trial methodology (7-9) and previously published discussions (10-12).

Medication Overuse in Chronic Migraine

The operational diagnostic criteria for chronic migraine (Appendix 2) are based on the most recently published International Classification of Headache Disorders (ICHD) (13).

Many patients with chronic migraine overuse acute medications (14-16) and also fulfill criteria for medication overuse headache (Appendix 3) (13). Though randomized controlled trials versus placebo or active comparator on large populations of medication overuse headache with long follow-ups are still lacking, there is persuasive evidence that withdrawal of overused drug(s) abates the number of days with headache in the majority of subjects for variable periods of time.

With these considerations in mind, in order to isolate and quantify the effect of the new drugs without preventing the possibility to access trials to a large and representative population of chronic migraine sufferers, in these guidelines we will allow the inclusion in trial of patients who are overusing medications for headache, provided that specific recommendations are followed (see paragraphs 1.1.1, 1.1.10, 1.1.2, 1.2.5).

For diagnostic purposes and in the clinical practice, chronic migraine and medication overuse headache should be diagnosed according to the most recent International Classification of Headache Disorders and treated accordingly. In particular, medication overuse headache should be dealt with overused drug withdrawal.
For the specific purposes of these guidelines, we will identify 2 subtypes of chronic migraine: chronic migraine with medication overuse and chronic migraine without medication overuse.

1 Drug trials for the prevention of chronic migraine

Double-blind, randomized, controlled trials are needed to establish efficacy for the preventive treatment of chronic migraine (see Section 1.2). Open-label and single-blind trials, which are limited by the influence of investigator-subject interaction on outcomes and placebo response, should not be used to assess efficacy, but they may be hypothesis-generating when combined with clinical observations. The treatment under evaluation must be compared with an appropriate control, such as placebo or sham, but an active comparator may be acceptable depending on the nature of the trial. In trials of preventive treatment of chronic migraine, the choice of an active comparator is limited to the only agents that have shown superiority over placebo: topiramate and onabotulinumtoxinA. When a drug under investigation has known side effects, the use of an active placebo is recommended to preserve blinding.

Controlled studies must be adequately powered to show a clinically relevant benefit versus placebo (see Section 1.3). Multi-centered studies have the advantages of avoiding the introduction of bias from a single site and offering access to an appropriate quantity and diversity of subjects. Underpowered studies may be

hypothesis-generating and may provide information on safety and tolerability, but they are not adequate for proving the efficacy of a new drug or biological.

All clinical trials must follow standardized ethical and safety guidelines; be approved by appropriate institutional review boards or ethics committees; be conducted in accordance with The Declaration of Helsinki (14) and Good Clinical Practice Guideline (15); follow rules in accordance with local regulatory authorities; and be pre-registered in an acknowledged trial register. Subjects must provide informed consent.

This recommendation addresses trial designs for data collection required by Health Technology Assessment (HTA) bodies. The IHS Clinical Trials Standing Committee also recommends post-approval prospective registries and open-label or observational studies to collect long-term data on efficacy, tolerability, and safety. These registries/studies may include subjects who were excluded from randomized trials, including individuals with comorbid and concomitant conditions and those using other drugs and treatments.

1.1 Selection of subjects

1.1.1 Chronic migraine definition

Recommendations:

The diagnostic criteria for chronic migraine used in controlled trials should comply with the latest available version of the ICHD. These guidelines are for adults with chronic migraine and do not apply to trials in children and adolescents.

1.1.1.1 Chronic migraine with medication overuse

Recommendations:

Subjects with chronic migraine meeting criteria for medication overuse at baseline may be included in the trials and stratified accordingly. No directions should be given on changing overused drugs for the screening phase, baseline, and the double-blind period to avoid confounding the outcome measures, unless it is required by the nature of the trial (eg, the trial investigates withdrawal regimens; see Section 1.2.8).

Comments:

Acute medication overuse is frequent in patients with chronic migraine (16-18), and it should be discouraged in clinical practice (19-21). Since discontinuation of overused drugs is associated with variable headache improvement, it is acceptable to include subjects with medication overuse in controlled trials if a stratified randomization procedure is used to optimize the chances that the treatment groups will be balanced for MO. Depending on the research question, subjects may be selected or stratified based on the type of medication overused (eg, triptans, analgesics, combination drugs).

This recommendation does not apply to subjects overusing barbiturate-containing analgesics, opioids, or subjects with medical conditions attributable to medication overuse (eg, peptic ulcer disease from overuse of nonsteroidal anti-inflammatory drugs [NSAIDS]), for whom adequate and careful discontinuation is strongly recommended prior to enrollment (21). While these subjects should be excluded from conventional clinical trials, they can be included in studies specifically designed to evaluate them.

If subjects with medication overuse are included in a trial, it is mandatory to record use of all headache medications during the baseline period and treatment phase. The number of days acute medications are taken and the specific medication(s) used. during the treatment phases needs to be captured and evaluated as a secondary or tertiary treatment outcome. Alternative trial designs may include subjects with frequent episodic migraine (10–14 headache days per month) and subjects with chronic migraine, with analyses performed on subgroups of the 2 patient populations. In this case, randomization should be stratified by the headache pattern (episodic/chronic) and the study should be adequately powered to identify whether there is a treatment effect in the EM, as well as, the CM population.

1.1.2 Other headaches

Recommendations:

Tension-type-like and migraine-like headaches are permitted under the criterion specifying at least 15 headache days per month (13), as long as subjects meet the ICHD criteria for chronic migraine. Other types of primary episodic headaches (eg,

primary stabbing headache) are permitted if subjects can clearly distinguish them from migraine attacks. Patients with secondary headache conditions should be excluded, except those with medication overuse headache (see Section 1.1.1.1).

1.1.3 Duration of disease

Recommendations:

Chronic migraine should be present for 12 months prior to evaluation for study inclusion, to minimize the inclusion of patients that may demonstrate regression to the mean and experience a spontaneous reduction in the frequency of attacks during the trial. The duration of episodic migraine should also be ascertained.

Comments:

Considering the spontaneous fluctuations in migraine frequency (22), requiring at least 6 months of chronic migraine will ensure that subjects enrolled into a clinical trial are less likely to enter a spontaneous remission period where they may experience fewer than 15 headache days per month.

1.1.4 Duration of observation

Recommendations:

A prospective baseline observation period of 4 to 8 weeks is recommended. Documentation is preferably performed via electronic headache diaries, as described in Section 1.1.12. This permits time-stamping of collected data and facilitates remote monitoring.

Comments:

Although the present chronic migraine definition requires at least 15 monthly headache days, the recommended time period of data collection for baseline and treatment periods in controlled trials is 4 weeks (28 days). Subjects having at least 14 headache days within 28 calendar days, with at least 8 days with migrainous features during the 28-day period, should qualify for a diagnosis of chronic migraine.

A prospective baseline observation period of 4 to 8 weeks is needed to establish baseline attack frequency and classify each headache day to ensure that at least 8 days meet criteria for migraine, probable migraine, and/or respond to triptans,

ergotamines, or other migraine-specific acute treatments. Headache characteristics (pain quality, intensity, location, and relationship with routine physical activity) and use of acute headache medication also need to be adequately assessed with a headache diary.

The baseline period allows investigators to screen for subject compliance by way of the diary. Patients who fail to fill in the diary for more than 6 non-consecutive days in a 28-day period should be excluded due to low compliance. Longer baseline periods provide a more stable 28-day baseline.

1.1.5 Age at onset

Recommendations:

The age at onset of episodic migraine should be younger than 50 years and the age of onset of chronic migraine should be younger than 65 years.

Comments:

Episodic migraine beginning after the age of 50 is very unusual (23), but chronic migraine may begin 8 to 10 years after episodic migraine (24). Note that the risk of headache associated with secondary causes or due to concomitant medication increases with age.

1.1.6 Age at entry

Recommendations:

Individuals who are at least 18 years of age may be entered into adult studies.

Comments:

Regulatory agencies require separate trials in children and adolescents. Development programs may include younger subjects. Special protocols are required for the inclusion of adolescents under the age of 18 (25, 26) in order to show efficacy, tolerability, and safety. Children younger than age 12 should be excluded from trials of treatments for chronic migraine for the following reasons:

- Chronic migraine is extremely rare in children
- Placebo response is very high in children

- Children should be exposed to new drugs only after safety has been established for a period of years in a large number of adult subjects
- A negative impact on a developing brain cannot always be excluded for a new drug
- Trials in children will be underpowered for efficacy

Guidelines for clinical trials of preventive treatment of chronic migraine in adolescents and children will be addressed in a separate document.

1.1.7 Enrollment

Recommendations:

Subjects should meet all predefined protocol inclusion criteria and not meet any of the predefined exclusion criteria. This needs to be documented at the time of baseline and randomization.

According to the Good Clinical Practice Guideline (15), subjects should be given a clear explanation of the purpose of the trial, as well as their role and the possible risks they may face by participating. The explanation must be formulated in a way that does not exaggerate placebo and nocebo responses. Obligations with which they must comply upon entry into the trial must also be clearly defined and explained.

Subjects who are allergic or have shown hypersensitivity to compounds similar to the trial drug should be excluded.

Comments:

Adherence to preventive treatment for migraine is often poor (27, 28), resulting in decreased efficacy. Therefore, subjects in controlled trials must be instructed in the importance of taking study medications exactly as directed, and adherence with protocol should be monitored via pill counts, e-diary reminders, and smart packaging.

Group characteristics regarding inclusion criteria should be reported. These include mean age; body mass index; age of migraine onset; age of chronic migraine onset; headache days; migraine days; use of concomitant preventive medications; days of

intake of acute medications; type and number of acute medications; presence of aura and presence of other primary headaches.

1.1.8 Sex

Recommendations:

Males and females should be included in clinical trials, ideally in a distribution that reflects the sex ratio of the population with chronic migraine.

Comments:

Females outnumber males with chronic migraine in the general population, and this preponderance may be exaggerated in controlled trials. As a result, efforts should be made to recruit male subjects in proportions that reflect the sex ratio in epidemiologic studies (29, 30).

With females, appropriate precautions should be taken to avoid enrolling those who are or may become pregnant because of inadequate contraception. Breastfeeding women should be excluded from studies of treatments with the potential for toxicity to the infant or when the potential for toxicity is unknown. Males need to use appropriate measures of contraception while in a trial with a new drug.

1.1.9 Coexistent disorders

Recommendations:

Subjects must be screened for coexistent (including psychiatric) conditions to exclude illnesses that may influence the conduct or results of the trial. Depending on the nature of the trial, the presence of some coexistent disorders may justify exclusion based on the potential for exacerbating an underlying condition or because the concomitant management of coexisting conditions may confound study results or make adherence and compliance with medications or trial obligations difficult (31). Subjects with coexisting conditions, such as depression, may be included if they are defined *a priori*, stable on current treatment regimens (with no anticipated changes in management that may interfere with study results), and recorded throughout the study.

Comments:

Major depression, anxiety, obesity, and chronic pain are common in patients with chronic migraine (32-34). Their presence, classification, and associated treatment needs must be assessed prior to study inclusion. When the treatment of subjects with these conditions may interfere with study drugs or the condition under study (chronic migraine), they should be excluded from participation. Other common reasons for exclusion include severe depression and overuse of alcohol or illicit drugs, as defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (35).

1.1.10 Concomitant drug use

Recommendations:

Studies of monotherapy are ideal for establishing the efficacy, safety, and tolerability of novel therapies. Given the nature of chronic migraine, however, a maximum of one concomitant preventive medication is allowed as long as it has been stable for at least 3 months before randomization and is not changed during the trial (36, 37). Randomization should be stratified by the use of concomitant preventive medication.

Comments:

The protocol should specify any concomitant medications that may or may not be used upon enrollment and/or during the trial.

1.1.11 Subjects who have already participated in previous headache trials

Recommendations:

Subjects should be prohibited from participating in more than 1 clinical trial at the same time. A trial extension (eg, long-term safety) is considered part of the same study. Concurrent participation in a controlled trial and prospective registries without treatment regimens is possible.

1.1.12 Data collection and monitoring

Recommendations:

Headache characteristics, use of medications, and compliance are best recorded by means of electronic diaries with time stamps, remote monitoring, and alerts. In settings where electronic diaries are not available, paper diaries are appropriate.

Adverse events (AEs) should be recorded in real time on the diary by the patient. Their characteristics and relation with the drug under investigation will be ascertained during follow-up visits or phone calls. Serious AEs (SAEs) need to be reported within 24 hours.

Comment:
It is important to minimize the response burden associated with diary information recording. It is also important to ensure that the time needed to complete each daily set of questions is similar regardless of whether subjects experience an attack.

1.1.13 Response to previous treatments

Recommendations:
Subjects who have previously failed preventive treatments can be included in clinical trials. Treatment failure is defined as any of the following: insufficient efficacy with adequate dosing and duration of treatment; intolerable side effects; contraindications precluding use; safety concerns.

Comment:
Insufficient efficacy, tolerability and safety can be ascertained via patient's report or communication with the treating physician.

1.2 Trial design

1.2.1 Blinding

Recommendations:
Controlled trials must be double-blind to establish efficacy, safety, and tolerability.

Comments:
Due to the placebo effect, controlled trials should be blinded or sham-controlled. Unblinding due to AEs may be a significant factor in placebo-controlled trials of preventive treatments of chronic migraine. During the trial, subjects and investigators may be asked to predict (best guess) whether subjects have been assigned to receive active treatment or placebo.

1.2.2 Placebo control

Recommendations:

Treatments used for the prevention of chronic migraine should be compared with placebo (or sham, as appropriate). When 2 presumably active drugs are compared, a placebo control can provide for a measure of additional assay sensitivity, if appropriate.

Comments:

The placebo effect in chronic migraine prevention studies is quite variable (38, 39). Higher rates are observed when the study drug/treatment is parenteral/invasive (40) or when there is an unequal randomization between active treatment and placebo (41).

Active treatments must demonstrate superiority to placebo. A trial showing that 2 presumably active treatments are equally effective does not necessarily prove the efficacy of either treatment.

1.2.3 Parallel-group and crossover designs

Recommendations:

Parallel-group designs are recommended. Crossover designs have many shortcomings, including fluctuations in treatment effects over time, carry-over effects, and challenges in the management of withdrawals and protocol deviations (42).

Comments:

Crossover designs have significant disadvantages. These include the possibility of a carryover effect, which cannot be controlled with certainty even with wash-out periods, and the need for a longer study duration, which may increase the likelihood that subjects will drop out of a trial.

There are several variations to the standard parallel-group trial methodology (e.g. cluster, non-inferiority, equivalence) (http://www.consort-statement.org/extensions). They have methodological features that differ from superiority trials and present some challenges in design, conduct, analysis, and interpretation. They might become useful in the future, when more data from standard superiority trials will become available.

1.2.4 Randomization

Recommendations:

Controlled trials require that subjects be randomized, preferably in relatively small blocks, after the baseline period. The process for randomization should be defined.

Comments:

Subjects are often recruited for trials of preventive treatment of chronic migraine over extended periods. Therefore, to ensure balanced randomization across treatment groups, it is preferable to randomize subjects in relatively small blocks (eg, 4-8 or 4-10) of varying size (43).

1.2.5 Stratification

Recommendations:

Stratified designs are recommended, where appropriate, in parallel-group trials.

Comments:

Randomization alone does not ensure that treatment groups will be balanced for factors that can influence treatment response. This is particularly true when sample sizes are modest. As sample size increases, randomization increasingly ensures that that treatment groups will be balanced for a particular confounder. Unbalanced treatment groups can spuriously alter study results.

There are 2 approaches for addressing this problem: including potential confounders in planned statistical analyses and stratified randomization. Incorporating potential confounders into planned statistical analyses simplifies study logistics and is the more widely used approach (see Section 1.4). With stratified randomization, the confounder is used to assign subjects to treatment groups and ensure that the groups are balanced. Stratified randomization should be considered for known confounders that are readily measured at baseline, such as the number of prior preventive medications or acute medication overuse, but it is difficult to do for multiple factors, and it complicates study logistics. For this reason, stratification needs to be limited to a certain number of factors that depend on sample size.

1.2.6 Baseline period

Recommendations:

A 28-day prospective baseline period using a headache diary that ensures subjects meet diagnostic criteria for chronic migraine is recommended. Other useful information that can be collected with a diary includes migraine associated symptoms and the acute medication usage (type and frequency), attack duration, attack severity, presence of aura, and impact on functional ability. Headache relief by individual acute migraine medications is based on subject's report and can be captured in the baseline period. Diaries should be electronic and feature time stamps (to reduce recall bias) and the option of remotely monitoring data entered by subjects.

Comments:

The baseline period should be used to confirm that enrolled subjects are eligible for study, demonstrate that they can adhere to data collection procedures, and provide baseline data for the primary outcome measures (10, 13, 38, 39, 44-47). The primary outcome variable for chronic migraine prevention studies is usually the change from baseline in migraine days or moderate/severe headache days. Because the change is calculated by subtracting headaches per unit time on treatment from headaches per unit time at baseline, the accuracy of the baseline assessment directly influences study results. Four weeks is the minimum recommended baseline period, though some studies have used baseline periods of as long as 12 weeks. Since attack frequency varies weekly and monthly in persons with migraine (48), longer baseline periods provide more accurate assessments of baseline status. A disadvantage is that long baseline periods may complicate enrollment, increase pre-randomization drop-out rates, and delay treatment for patients with unmet treatment needs. High variability in baseline frequency estimates for primary efficacy measures diminishes statistical power. Inclusion and exclusion criteria need to be carefully considered prior to the baseline period to minimize the variability of the parameter across the study population.

1.2.7 Duration of treatment periods

Recommendations:

A minimum treatment period of 12 weeks is recommended. Trials of 24 weeks may be useful in evaluating cumulative benefit and persistence of efficacy while also providing additional safety and tolerability data. A long-term observational period to collect additional safety data should be considered, where appropriate.

Comments:

Longer treatment periods increase the power of the trial by providing more stable estimates of outcome measures. The efficacy of many treatments accrues gradually, with some medications needing up to 24 weeks before their full preventive potential is realized. The limitation of a longer randomization phase is that subjects remain on placebo for an extended period, increasing their risk of discontinuation (especially for lack of efficacy). If a treatment has a rapid onset of action and does not require dose titration/escalation, a shorter treatment period (8 weeks) may be appropriate. A long-term observation period may help identify additional AEs or time to relapse. In trials of drugs that are not yet approved, an open-label, long-term extension study can provide subjects who participated in the placebo arm of a controlled trial with access to a novel therapy while collecting useful information about safety and adherence to treatment.

1.2.8 Post-treatment period

Recommendations:

After termination of the randomized treatment period, subjects should be followed prospectively for a period of time depending on the substance under investigation for the evaluation of safety. Ideally, they should continue to complete a daily diary during this period.

Comments:

Randomized withdrawal trials can be considered (49). In withdrawal studies, all subjects initially receive active treatment. After 12 weeks, subjects are randomized in a blinded fashion to continue active treatment or placebo. Trials employing this design may identify rebound phenomena and modification of chronic migraine that may occur after the termination of active treatment.

1.2.9 Dosage or procedures

Recommendations:

In phase II trials, attempts should be made to test as wide a range of dosages as appropriate (eg, minimal effective dose and maximum tolerated dose). In phase III trials, 2 or more doses can be selected.

Comments:

If the basis for the efficacy of preventive treatment remains unknown, the choice of dosages and/or intensity of intervention is a purely empirical compromise between observed efficacy and tolerability.

1.2.10 Acute headache medication and concomitant headache treatment

Recommendations:

Acute treatment of migraine attacks must be allowed. However, it is important that acute treatments remain the same throughout the baseline period and for the duration of the trial. Likewise, preventive migraine medications with established efficacy or a probable influence on treatment outcomes should neither be started nor discontinued during the trial. Similar restrictions should be applied to devices and non-pharmacological treatments that have proven efficacy in migraine prevention (eg, non-invasive vagal stimulation, occipital nerve stimulation, stress management) or are likely to alter the outcome (eg, acupuncture, physical therapy, occipital nerve blocks, and onabotulinumtoxinA). Intake of acute medication needs to be documented in the diary.

Comments:

Subjects must be allowed to use acute headache medication during the trial. Before the start of the baseline period, subjects should have their acute treatment optimized. During the baseline and randomization phases, subjects should be counselled not to change the type, dosage, or formulation of acute medication or the strategy by which it is taken (during mild pain versus moderate/severe pain). Subjects should be allowed to modify the frequency or use (eg, to medicate their headaches) in an unrestricted manner (eg, to increase or decrease the use of such treatments based on their own need). Any instruction on acute medication usage needs to be standardized across treatment centers to avoid confounding the interpretation of

study results. In controlled trials of preventive treatment of chronic migraine, complications may arise if frequent users of acute medications are counselled to taper or restrict their intake, or some subjects switch their acute medication from a simple analgesic to a triptan. In either case, a change not carried across the total cohort has the potential to confound the interpretation of pre-specified outcome measures.

1.2.11 Control visits

Recommendations:

Subjects should be followed regularly during the trial. Subjects are usually seen at the time of screening, beginning and end of baseline, and after randomization/initiation of treatment. Subsequent visits are contingent upon the treatment being tested and the duration of the trial. Face-to-face visits are recommended every 4 to 8 weeks. Telephone or video contacts can be used in between, and remote monitoring methods should be encouraged to improve adherence.

Comments:

Regular contact with subjects participating in clinical trials is important for determining eligibility, ensuring adherence, and monitoring for AEs.

1.3 Evaluation of endpoints

Recommendations:

All primary and secondary endpoints need to be prospectively defined, with specific comparative groups defined (ie, treatment vs placebo or vs baseline) and time points identified (ie, 4-week or 12-week), and they should depend on study objectives. Power calculations for the primary and the most relevant secondary endpoints need to be performed prior to study initiation.

Comments:

Issues with analysis of multiple comparisons may arise with the use of multiple primary endpoints or 3 or more treatment groups. In the case of multiple primary endpoints, multiplicity issues can be avoided by proposing a composite endpoint or using hierarchical testing procedures. Should investigators decide to use a multiple

comparison adjustment, it needs to be reflected in the calculations of sample size and statistical power.

There are some issues with the use of composite endpoints that must be considered. It is important that each of the component s are by themselves clinically relevant and sufficient to establish treatment benefit, as success of the composite may be driven by any of the components. Also, composite endpoint may be problematic, for example, in a case where there is not a consistent response for each of the components of the composite or when findings for the composite endpoints move in different directions (some positive others negative).

1.3.1 Primary endpoints

Recommendations:

The primary endpoint in controlled trials of preventive treatment of chronic migraine should be either change in migraine days; change in moderate to severe headache days; or responder rate. From these 3 endpoints, the 2 not selected as the primary endpoint should be considered as secondary endpoints.

Evaluations of efficacy should be based on information obtained from headache diaries. For multinational trials, diary design should be standardized, with translations adapted to the linguistic and sociodemographic characteristics of target populations.

1.3.1.1 Definition of migraine day

A migraine day is defined as a day with a headache that lasts at least 4 hours; meets ICHD-III criteria C and D for migraine without aura (1.1), B and C for migraine with aura (1.2), or ICHD-III criteria for probable migraine (1.6); or a day with a headache that is successfully treated with a triptan, ergotamine, or other migraine-specific acute medication.

1.3.1.2 Definition of moderate/severe headache day

A moderate/severe headache day is defined as a day with moderate or severe pain that lasts at least 4 hours or a day with a headache that is successfully treated by an acute headache medication.

These definitions allow the use of a relatively simple headache diary. Subjects indicate whether a headache was present (yes/no), its peak severity (mild/moderate/severe) and duration (<4 h or ≥4 h), acute medication intake type (triptan/ergotamine/other) and migraine associated symptoms. Response to treatment should also be recorded.

1.3.1.3 Definition of responder rate

The responder rate is calculated as a percent reduction from baseline in the number of migraine days or number of moderate or severe headache days in each treatment period. Responder rates in chronic migraine trials have traditionally been defined as at least a 50% reduction from baseline, but other percent reductions (eg, 30%, 75%, and 100%) may be used. Specific responder rates used in controlled trials must be prospectively defined.

Responder rates can be used in meta-analyses of placebo-controlled, randomized, controlled trials. They should not be used to judge whether individual patients are experiencing clinically meaningful treatment effects in clinical practice.

Comments:
The recommended time period for analyses in 12-week trials is preferably the entire treatment period, although the analysis of the last 28 days may be helpful for capturing a slow-onset effect of the drug. In 24-week trials, the recommended period for analysis is the last 12 weeks. Alternatively, results over the entire period may be considered in a sensitivity analysis.
A migraine day or a moderate to severe headache day is defined as a time period of less than 24 consecutive hours over 1 or more calendar days (eg, a headache starting at 20:00 and ending at 01:00 the next morning should be counted as a single migraine or headache day). Exceptions may apply in specific circumstances, such as when an attack is interrupted by sleep.

Because cross-study comparisons may be complicated by differences in how migraine and headache days are defined, it is critical that these endpoints be prospectively defined.

1.3.2 Secondary endpoints

The secondary endpoints listed below are organized based on the components they explore (ie, not in order of priority).

1.3.2.1 Headache-related

1.3.2.1.1 Moderate/severe headache days

May be used if not chosen as the primary endpoint.

1.3.2.1.2 Migraine days

May be used if not chosen as the primary endpoint.

1.3.2.1.3 Responder rate

May be used if not chosen as the primary endpoint.

1.3.2.1.4 Intensity of migraine

A categorical, 4-point rating scale should be used to rate each migraine day as absent, mild, moderate, or severe. Intensity alone is not recommended as a primary outcome measure, but it is important to record a decrease in migraine intensity as an indicator of reduced disability. Depending on the trial design, subjects should be instructed to record the intensity of each migraine day. An 11-point Visual Rating Scale (VRS) can be used as an alternative to or in association with the 4-level categorical rating scale. Use of the VRS in clinical trials may increase the likelihood of being able to show a difference in severity (50).

1.3.2.1.5 Intensity of headache

A categorical, 4-level rating scale should be used to rate each headache as absent, mild, moderate, or severe. As in the case of migraine days, intensity alone is not recommended as a primary outcome measure. Intensity of headache is integrated into the primary outcome measure of number of headache days with moderate or severe intensity. These are the most disabling attacks. Depending on the trial design, subjects should be instructed to record the maximum intensity for each headache day. An 11-point VRS can be used as an alternative or in association to the 4-level

categorical rating scale. Use of the VRS scale in clinical trials may increase the likelihood of being able to show a difference in severity.

1.3.2.1.6 Cumulative hours per 28 days of moderate/severe pain

This can be easily calculated with electronic diaries and may be meaningful for patients. If a subject goes to sleep with headache and wakes up with headache, the time period in between is counted as headache hours.

1.3.2.1.7 Conversion to episodic migraine

Defined as the proportion of subjects with fewer than 14 migraine or headache days per 4 weeks over a 12-week period.

1.3.2.1.8 Onset of effect

Understanding the onset of action of preventive treatments may help to refine management strategies. The onset of effect can be captured by specific analyses in the first weeks of treatment.

1.3.2.2 Acute headache medications

1.3.2.2.1 Acute treatment utilization

The use of acute migraine medication must be recorded, including the number of days and the specific drug used. It is imperative that subjects do not receive any special counsel to change the frequency of use of acute headache medications during the treatment phase, so that any fluctuation in their use (either increase or decrease) can be evaluated.

1.3.2.2.2 Conversion of medication overuse to non-medication overuse

The absolute number and percentage of subjects who cease overuse of acute medications in the last 12 weeks of a 24-week trial should be captured using the diaries.

1.3.2.3 Depression and anxiety

Depression and anxiety levels should be recorded at the time of randomization and at the end of the double-blind treatment period.

1.3.2.3.1 Validated scales for depression

Validated scales for depression in migraine include: Patient Health Questionnaire-9 (PHQ-9) (51), Patient Health Questionnaire-4 (PHQ-4) (52), Beck Depression Inventory (BDI) (53), Hospital Anxiety and Depression Scale (HADS) (54).

1.3.2.3.2 Validated scales for anxiety

For anxiety, besides HADS, the State-train Anxiety Inventory (STA-I) (55) and the Generalized Anxiety Disorder (GAD-7) (56) can be used.

1.3.2.4 Patient's reported outcome measures

1.3.2.4.1 Patient Global Impression of Change

The Patient Global Impression of Change scale (PGIC) (57) can be used to evaluate subject satisfaction as a secondary endpoint.

1.3.2.4.2 Functional Impairment Scale

The Functional Impairment Scale (FIS) is a 4-point scale that addresses functional status and intensity of impairment during daily activities (4, 58) that can be used in conjunction with the 4-point pain intensity scale.

1.3.2.4.3 Migraine Functional Impact Questionnaire

The Migraine Functional Impact Questionnaire (MFIQ) is a 26-item self-administered instrument for the assessment of the impact of migraine on physical functioning, usual activities, social functioning, and emotional functioning over the past 7 days (59).

1.3.2.4.4 Other

Other patient reported outcome instruments may be used as they are validated.

Comments:

The use of subjects' preferences is not recommended as an efficacy measure, but it is important to evaluate the well-being of study subjects, and it is useful to define

clinically meaningful changes. Subject preferences for 1 or another treatment can be assessed only in a crossover trial.

1.3.2.5 Exploratory outcome measures

In addition to primary and secondary outcome measures, these measures can be used to capture outcomes that may be clinically meaningful and correlate with primary/other secondary endpoints.

1.3.2.5.1 Number of symptom-free days

These are defined as the days free of premonitory, aura, headache, and postdromal symptoms. They are best quantified through the headache diary.

1.3.2.5.2 Number of headache-free days

Days with no headache, associated symptoms, including physical function, cognitive or emotional impairment that is directly attributable to migraine.

1.3.2.5.3 Other

Other interictal burden outcome instruments may be used as they are validated.

1.3.2.6 Healthcare outcomes/quality of life

Validated, disease-specific health-related quality of life (HRQOL) and disability instruments are recommended as secondary endpoints. For some of the instruments listed in this section, the between-group minimal important difference (MID) has already been defined in migraine and used in trials on chronic migraine (60-62).

1.3.2.6.1 Migraine-Specific Quality of Life questionnaire

The Migraine-Specific Quality of Life questionnaire (MSQ v2.1) is recommended to evaluate the change in quality of life related to chronic migraine (63).

1.3.2.6.2 Headache Impact Test

The Headache Impact Test (HIT-6) (64) is recommended for capturing migraine-related disability with a 1-month recall period. Note that HIT-6 needs to be licensed.

1.3.2.6.3 Migraine Disability Assessment questionnaire

Also recommended for capturing migraine-related disability, the Migraine Disability Assessment (MIDAS) questionnaire (65) measures a 3-month recall period.

1.3.2.6.4 EuroQoL-5 Dimension Questionnaire

EuroQoL-5 Dimension Questionnaire (EQ-5D) is a self-administered standardized measure of health status (66, 67). Registration is needed to use this instrument.

1.3.2.6.5 Short Form 36-Item Health Survey

The Short Form 36-Item Health Survey (SF-36) represents a generic instrument for the evaluation of quality of life (68).

Comments:
Health-related quality of life, which represents the net effect of an illness and the impact of therapy on a subject's perception of their ability to live a useful and fulfilling life (69, 70), can be measured with generic and/or specific questionnaires. Generic questionnaires are usually chosen to compare study populations with different diseases, whereas disease-specific questionnaires are designed to assess problems associated with a single disease or treatment. Disease-specific instruments are more likely to be sensitive to change in a treatment trial. Instruments for measuring HRQOL in chronic migraine must be scientifically developed and standardized. No single instrument is currently recognized as the gold standard in migraine HRQOL assessment. For chronic migraine, there are no disease-specific instruments, but the instruments used for episodic migraine have performed well in capturing the impact of chronic migraine (71).

For HRQOL endpoints to be valid, it is also important that instructions and education on lifestyle factors (eg, sleep hygiene, diet, caffeine use, exercise, etc.) are consistent among treatment groups and across study centers. The same applies to behavioral treatments (eg, cognitive therapy, biofeedback). If these methods are included in the study design, they should be defined *a priori* and standardized to avoid confounding study outcomes.

1.3.3 Pharmacoeconomic endpoints

Recommendations:

The economic value of preventive treatment for chronic migraine should be assessed in studies that capture both the costs of medical treatment (direct costs) and lost productivity (indirect costs).

Work productivity and activity represent important components of disability and chronic migraine-associated costs. The mean change from baseline can be measured by the Work Productivity and Activity Impairment (WPAI) instrument (72). A migraine-specific version of the WPAI has been developed and can be found on the developer's website (73); validation studies are ongoing.

Comments:

The high cost of chronic migraine to individual sufferers and society may be offset or reduced by effective preventive treatment. The costs of medical treatment can be estimated using diaries or electronic data before and after treatment. Lost productivity (eg, work, household work, other activities) can be measured with self-reported diaries, through experience-based sampling, using employer work records, or by MIDAS questionnaire. Demonstrating that treatments for chronic migraine are effective and cost-effective will support the development and implementation of health policies that prioritize chronic migraine.

1.3.4 Adverse events

Recommendations:

Documentation of AEs and SAEs during treatment should follow local institutional review boards, regulatory authority guidelines, and Good Clinical Practice Guidelines. Acceptable methods include spontaneous reports recordings, open-ended questions, and direct questioning. Adverse events should be reported separately for active and placebo treatment.

Comments:

Adverse events often occur before maximum efficacy is reached. In clinical practice, AEs are a major problem in preventive migraine treatment, often leading to discontinuation of treatment. The incidence of AEs, especially those leading to

discontinuation of treatment, should be regarded as 1 of the major measures of the tolerability of a preventive migraine treatment.

Adverse events are not necessarily related to treatment. They should be recorded openly in order to detect any unexpected and unwanted effects during the development program of a drug. Investigators need to indicate whether the AEs are treatment-related. It should be noted that regulatory authorities require more detailed reporting of AEs with new experimental treatments (74, 75).

1.4 **Statistics**

Recommendations:

Issues that need to be defined *a priori* in preplanning the analysis of data for chronic migraine studies include:

- Primary measurement time
- Statistical analysis plan
- Primary efficacy variable
- Modalities of data collection (to evaluate a change in efficacy variables); for example, if moderate/severe headache days are being evaluated, the record of occurrence, start and stop time, duration of headache, and minimum duration required for counting the headache day (ie, ≥4 hours) are all individual outcomes that should be defined and captured
- Target sample size needed to achieve appropriate power for statistical significance among treatment groups must be defined
- Comparisons between the treatment phase and baseline phase as primary endpoints, secondary endpoints, or both
- The rules for the imputation of missing data for designated variables; for example, if the headache stop-time is to be captured but is unknown, a decision rule might be to assume that the headache stopped at the end of the last day (eg, 23 hours and 59 minutes) that it was reported to be ongoing
- The methodology for comparisons between treatment groups
- The analysis population

Comments:

In general, subjects should be analyzed according to the randomization assignment, regardless of actual treatment received (ie, intent-to-treat population, analyzed as randomized). For safety variables, it may be reasonable to analyze subjects according to the treatment the subject actually received (ie, safety population, analyzed as treated). In order to have data for all subjects in the intent-to-treat population, it is possible to impute missing data for at least the primary variable of interest, either as a primary analysis or as a sensitivity analysis. Alternate statistical methods may be used if verified by a statistician.

Summary tables for each treatment and for each measurement time should include the number of subjects and descriptive statistics (mean, standard deviation, median, minimum, and maximum) and/or response frequencies.

Statistical analyses are based on certain assumptions, and statistical plans need to employ methods and tests designed to evaluate them. In addition, investigators need to propose an alternative analysis plan if any assumptions are not met. For example, if normal distribution assumptions are not met by the data collected as a part of the current study, then analysis would be done using Wilcoxon rank sum test instead of a 2-sample t-test. Normality assumption can be checked using various tests or graphic methods readily available in statistical software (eg, SAS®).

Randomization does not always guarantee that treatment groups will be balanced on all baseline characteristics. If such imbalances are observed for key variables of interest, then analysis needs to be performed using regression methods. To improve evaluations of the efficacy of different interventions, the effect size for the primary outcome measure(s) should be calculated with available statistical methods. This approach will also facilitate comparisons of findings from different studies (76, 77).

1.5 **Trial registration**

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

1.6 **Publication of results**

Publication in manuscript form of all research results (primary and secondary endpoints and all safety data), either positive or negative, is necessary.

At the time of study initiation or at the end of recruitment, a design paper with baseline data may be published. Before the study is initiated, investigators and sponsors (if applicable) should agree upon timelines for publication; ideally, they should form part of the protocol. A publication committee should be formed prior to the start of the study.

Authorship should be based on the recommendations of the International Committee of Medical Journal Editors (78).

1.6.1 Conflict of interest

For sake of transparency, all authors must declare their conflicts of interest. A conflict of interest exists whenever professional judgment concerning a primary interest (such as patients' welfare or the validity of research) may be influenced by a secondary interest (such as a financial tie to the sponsor).

Financial ties that represent potential conflicts of interest include employment, consultancies, grants, fees and honoraria, patents, royalties, stock or share ownership, and paid expert testimony. Conflicts of interest usually extend to an investigator’s spouse and children. Their presence is likely to undermine the credibility of the study. 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.

1.7 Independent Data Safety Monitoring Board

An independent data safety monitoring board and predefined stopping rules for futility or safety are recommended for phase III trials initiated after the publication of these guidelines.

1.8 Steering Committee

For phase III trials sponsored by industry, a steering committee comprised of academics, statisticians, and company representatives (where appropriate) is recommended. For investigator-initiated trials (ie, studies developed and sponsored by independent investigators or academia), a steering committee is not necessary. Whether or not a committee is used, investigators and sponsors are responsible for study conception, design, operational execution, data handling, data analysis and interpretation, subsequent reporting and publication, and ensuring compliance with all local laws and regulations.

2 Post-approval registries

The IHS recommends prospective post-approval registries, open-label or observational studies, to evaluate newly approved drugs and biologics in clinical practice. Registries generate data on long-term efficacy, tolerability, and safety. They also measure compliance and adherence and may provide information about withdrawal. Registries may also include patients with relevant co-morbidities (eg, chronic pain syndromes, cardiovascular disease) who were excluded from controlled trials.

3 Health Technology Assessment

In some countries, HTA bodies require dedicated studies for cost-effectiveness and calculation of a cost-benefit ratio as a precondition to granting reimbursement. For the purpose of these studies, healthcare costs associated with office and emergency department visits, diagnostic tests, hospital admission, and medication must be collected; working days lost (ie, the total number of days off work due to illness or injury) may also be measured. Some HTAs may require a comparison with an approved drug treatment.

4 Methodology used for the development of these guidelines

The IHS Clinical Trials Standing Committee developed the present edition of the Guidelines for Controlled Trials of Preventive Treatment of Chronic Migraine in Adults as an update to the 2008 edition (6). Using the framework of the 2008 edition, the Committee integrated almost a decade of new knowledge and literature in the field of Headache Medicine (Appendix 1) into its revision.

The Committee's work was independent and unbiased, and the process of developing this edition of the Guideline involved 3 phases. First, the Committee reviewed the 2008 Guidelines; evaluated the full evidence base, with emphasis on findings produced since 2008; and developed proposed revisions. Once an initial draft of the revised Guidelines was in place, the Committee shared it with representatives of the European Medicines Agency, the US Food and Drug Administration, pharmaceutical manufacturers, and patient associations; asked them to review the proposed changes; and invited their comments and suggestions in 2 face-to-face meetings. After incorporating the views of these stakeholders, the Committee posted the revision on the IHS website (http://www.ihs-headache.org/ichd-guidelines) in September 2017, called for comments from IHS members, and incorporated member comments to finalize this edition. Throughout the comment and revision periods, the Committee provided written replies to queries and observations as required.

Acknowledgements

The Authors are grateful to Jay Mandrekar, Professor of Biostatistics and Neurology Director, Biostatistics Core, Mayo Clinic, for his qualified and precious assistance in the preparation of the paragraph on Statistics.

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