

REVIEW

Guidelines for controlled trials of prophylactic treatment of chronic migraine in adults

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In 1991 the Clinical Trials Subcommittee of the International Headache Society (IHS) developed and published its first edition of the Guidelines on controlled trials of drugs in episodic migraine because only quality trials can form the basis for international collaboration on drug therapy, and these Guidelines would 'improve the quality of controlled clinical trials in migraine'. With the current trend for large multinational trials, there is a need for increased awareness of methodological issues in clinical trials of drugs and other treatments for chronic migraine. These Guidelines are intended to assist in the design of well-controlled clinical trials of chronic migraine in adults, and do not apply to studies in children or adolescents. □ *Chronic migraine, clinical trials, headache, medication-overuse headache, prophylactic treatment*

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Chronic migraine (CM) was originally classified in the International Classification of Headache Disorders (ICHD)-2, but due to the inability to classify most subjects in clinical practice, the criteria have been revised (CM-R, A1.5.1) to reflect more accurately the population of patients routinely seen in practice and, thus, the subjects who will be enrolled into clinical trials (1, 2). The current operational diagnostic criteria for CM-R (3) include:

- A. Headache on ≥ 15 days/month for at least 3 months.
- B. At least five attacks fulfilling criteria for migraine without aura (ICHD-2 1.1).
- C. On ≥ 8 days/month for at least 3 months headache has fulfilled C1 and/or C2 below:
 1. Has at least two of a–d (below):
 - a. unilateral location;
 - b. pulsating quality;
 - c. moderate or severe pain intensity;
 - d. aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs) and at least one of a or b (below):
 - (a) nausea and/or vomiting;
 - (b) photophobia and phonophobia;

2. Treated and relieved by triptan(s) or ergot before the expected development of C1 above.
- D. No medication overuse (as defined below) and not attributed to another causative disorder.

The criteria for medication-overuse headache (MOH (4)) have also been revised (MOH-R, A8.2) as the following (3):

- A. Headache present on ≥ 15 days/month.
- B. Regular overuse for > 3 months of one or more acute symptomatic drugs:
 1. Ergotamine, triptans, opioids or combination analgesic medications on ≥ 10 days/month on a regular basis for > 3 months.
 2. Simple analgesics or any combination of ergotamine, triptans, analgesics or opioids on ≥ 15 days/month on a regular basis for > 3 months without overuse (≥ 10 days) of any single class alone.
- C. Headache has developed or markedly worsened during medication overuse.

In 1991 the Clinical Trials Subcommittee of the International Headache Society (IHS) developed and published its first edition of the Guidelines on controlled trials of drugs in episodic migraine (5) because only quality trials can form the basis for international collaboration on drug therapy, and these Guidelines would 'improve the quality of controlled clinical trials in migraine' (6). More recently, this Committee published similar guidelines for tension-type headache (7) and cluster headache (8), and a second edition for migraine was published (6).

With the current trend for large multinational trials, there is a need for increased awareness of methodological issues in clinical trials of drugs and other treatments for CM. Recent studies on the efficacy of migraine-preventive therapies for CM have been published (9, 10); therefore, new studies need to be consistent in study design, patient population selection and data analysis in order to establish the necessary evidence-based treatment recommendations for subjects with CM. These guidelines are intended to assist in the design of well-controlled clinical trials of CM in adults, and do not apply to studies in children or adolescents. For discussion of issues applying to clinical trials in general, the reader should consult general works on clinical trial methodology (11–14) and general discussions published elsewhere on these issues (15–22).

1. Drug trials dealing with chronic migraine prophylaxis

The subjective nature of headache and a high placebo response rate makes interpretation of open- and single-blind trials difficult. However, such trials, as well as clinical observation, may be hypothesis-generating for possible prophylactic effect in CM; but double-blind, randomized, controlled trials are required to support proof of efficacy (23). The treatment being tested should be compared with placebo (or sham treatment when relevant). In episodic migraine, an established active comparator is often used to ensure model sensitivity; unfortunately, there is no approved or well-accepted standard for an active comparator for CM trials.

In placebo-controlled trials of CM, the treatment should be demonstrated to be better than placebo to a statistically significant extent in at least two studies. The number of subjects needed (see criteria below) often requires involvement of multiple centres. If enough subjects cannot be recruited, it is better to avoid doing placebo-controlled or comparative trials with insufficient power to establish efficacy or superiority, because the trial may only provide little more than tolerability information.

All clinical trials in CM must follow standardized ethical and safety guidelines. Studies must be approved through appropriate Institutional Review Boards (IRB) or ethics committees; subjects must provide informed consent; studies must be in accordance with The Declaration of Helsinki and follow rules in accordance with local regulatory authorities; and all clinical trials must be in accordance with Good Clinical Practice Guidelines.

1.1 Selection of subjects

1.1.1 Chronic migraine definition

Recommendations:

The diagnostic criteria for CM should comply with those of the revised appendix ICHD-2 (CM-R) criteria (3). These guidelines are for adults with CM-R and do not apply to studies in children.

1.1.1.1 Chronic migraine with MOH

Recommendations:

Subjects meeting criteria A–C but not criterion D of CM-R (i.e. MOH-R are also met) may be included in the trials for CM (3). However, subjects with MOH-R must be stratified accordingly.

Comments:

More subjects can be classified using the new appendix ICHD-2 criteria for CM-R. Requirements are more rigid for clinical drug trials than in clinical practice. This will involve excluding some subjects with ICHD-2 classification from clinical trials when implementing the appendix ICHD-2 criteria for CM-R (3). However, due to the high prevalence of acute medication use of > 10 days in migraine subjects with frequent headache, these subjects can be included only if they are stratified between active and placebo groups. Depending on the nature of the trial and number of subjects included in the trial, subjects may be selected or stratified based on type of medication overuse (e.g. triptans, opioids, caffeine, analgesics, etc.). Subjects requiring detoxification (e.g. from butalbital or opioid drugs) should not be included in these trials (unless detoxification is a specific part of that study protocol) due to safety concerns.

Should subjects with medication overuse be included in the trial, it will be important to record use of all medications during the baseline period and treatment phase. Should the subjects require less acute medication during the treatment phase, this can be captured and evaluated as a treatment outcome if defined *a priori*. No counsel, guidance or direction should be given on changing the type or frequency of acute medication use in this subgroup during the trial.

*1.1.2 Other (non-migrainous) headaches**Recommendations:*

Other headache types, such as tension-type, or probable migraine, are permitted as part of the ≥ 15 days/month as long as the subject meets CM-R criteria (= 8 days of ICHD-2 migraine without aura, or successfully treats a headache of any type with a triptan or ergot).

*1.1.3 Duration of disease**Recommendations:*

CM should be present for at least 6 months prior to evaluation for study inclusion.

Comments:

There are no objective signs of CM; therefore, a minimum course of 6 months duration is advisable. This will help exclude headaches from other disorders and ensure that subjects enrolled into a clinical trial are less likely to enter a remission period where they may experience < 15 headache days per month.

*1.1.4 Duration of observation**Recommendations:*

There should be a prospective baseline observation period of at least 1 month, which should include use of a headache diary.

Comments:

The character and especially frequency of headaches reported retrospectively by the subject may be different when carefully and prospectively observed by the physician and subject. Prospective observation will best define the baseline frequency and classify each headache day to ensure that at least 8 days meet criteria for migraine without aura and/or respond to treatment with a triptan or ergot.

*1.1.5 Age at onset**Recommendations:*

The age at onset of CM should be < 60 years.

Comments:

Episodic migraine beginning after the age of 50 is rare (< 2%). However, CM often begins 8–10 years after episodic migraine; therefore the age of onset can be later. Additionally, in CM the risk of headache associated with secondary causes increases with age, so this upper limit may reduce the risk of including subjects with secondary headache.

*1.1.6 Age at entry**Recommendations:*

Subjects may be entered into adult studies that are ≥ 18 years of age.

Comments:

Development programmes, at some point, may include younger subjects; however, at this time, special protocols are required for inclusion of children and adolescents under the age of 18 (24) in order to show efficacy as well as safety. At this time there are no established diagnostic criteria for CM in children.

*1.1.7 Enrolment**Recommendations:*

Subjects should meet all predefined protocol inclusion criteria, and not meet any of the predefined exclusion criteria. Subjects should be given a clear explanation of the purpose of the trial and their role in it. Obligations with which the subjects are expected to comply upon entry into the trial need to be clearly defined and explained to the subject (e.g. completion of a daily headache diary, following the instructions for consumption of the study medication, showing up for study visits, etc.).

Comments:

There is evidence that compliance with episodic migraine prophylactic drugs is often poor (25), and their efficacy may be restricted because of this.

*1.1.8 Gender**Recommendations:*

Both men and women should be included.

Comments:

There are more women than men in the general CM population. In most migraine trials, however, this female preponderance is exaggerated. Efforts should be made therefore to recruit men to an extent that reflects its epidemiological prevalence (26–31).

In studies including women, appropriate precautions should be taken to avoid treating those who are pregnant, may become pregnant because of inadequate contraception, or are lactating (unless this is the purpose of the study).

*1.1.9 Coexistent disorders**Recommendations:*

Subjects should be screened for coexistent medical and psychiatric disorders, which may have an impact on the trial. Depending on the nature of the trial, some coexistent disorders may be reason for exclusion because concomitant management of these coexisting conditions may confound study results. Coexisting conditions, such as depression, may be included if they are either defined *a priori*, stable on current treatment regimens (with no changes of management that may interfere with study results, such as antimigraine therapies), and stratified across treatment groups.

Comments:

Major depression, anxiety, obesity, hypertension and epilepsy are common in patients with migraine or CM (32), and diagnosis and treatment needs must be carefully assessed prior to study inclusion. For example, patients with hypertension requiring β -blocker treatment may be excluded because β -blocker treatment has proven efficacy for migraine prevention.

*1.1.10 Concomitant drug use**Recommendations:*

Studies of monotherapy are recommended. Adjunctive (add-on) therapy trials may be appropriate in subjects with intractable CM (33–35).

In monotherapy trials, the following should be followed:

- A. No other drugs of accepted (or proven) efficacy in the preventive treatment of episodic or chronic migraine should be allowed during the course of the trial.
- B. Exclude subjects who:
 1. abuse alcohol or other elicit drugs (DSM-IV criteria (36));
 2. are allergic or have shown hypersensitivity to compounds similar to the trial drug;
 3. are potentially fertile and sexually active women who do not use adequate contraception.
- C. Concomitant therapy may be permitted or discontinued depending on the nature of the trial.
- D. Carry-over effects of discontinued medications or treatments must be eliminated prior to randomization. If wash-out is required prior to entering the baseline period, then 1 month completely off the treatment, or at least 1 month after the therapeutic effect of the treatment has presumably resolved, is needed.

Comments:

It is desirable to eliminate subjects who overuse or abuse drugs or alcohol. Wash-out may not be needed in add-on trials. In these trials and to minimize a potential carry-over effect, previous preventive medication must remain stable for at least 3 months prior to the baseline period, and the dosage should remain stable during the treatment phase. The protocol should specify any concomitant medications that are not permitted for use upon enrolment and/or during the trial. Like acute medications, caffeine consumption should be documented at baseline and during the treatment phase but consumption cannot be regulated as this maneuver will be unbalanced across the treatment and placebo groups and regulating caffeine consumption may confound the result.

1.1.11 Subjects who have already participated in previous headache trials

It is recommended that the same subjects are not included in more than one clinical trial for the same treatment, with the exception of an add-on trial with a study period that immediately follows the previous trial (e.g. add-on long-term safety trial).

*1.2 Trial design**1.2.1 Blinding**Recommendations:*

Controlled trials should be double-blind.

Comments:

Unblinding may be a significant factor in acute and prophylactic placebo-controlled migraine trials. Subjects and investigators should be questioned at the end of the trial regarding their opinion as to what treatment group (active or placebo) the subject was assigned to during the study.

*1.2.2 Placebo control**Recommendations:*

Treatments used for CM prophylaxis should be compared with placebo (or sham intervention, as appropriate). When two presumably active drugs are compared, placebo control also should be included in order to test the reactivity of the subject sample.

Comments:

The placebo effect in episodic migraine prophylaxis is usually in the 20–40% range, and in some trials it has been even higher (37). A treatment, therefore, must be demonstrated to be superior to placebo. If two presumably active treatments are found equally effective in a trial, this is not necessarily proof of efficacy of either treatment. Using an established drug as a comparator group uses historical controls, a method largely discouraged in clinical trials. Both treatments should be shown contemporaneously to be superior to placebo.

*1.2.3 Parallel groups and crossover designs**Recommendations:*

At this point in time, parallel-group designs are recommended; the value of crossover design is uncertain, as studies of such design are rarely done.

Comments:

The limitations of the crossover design are (37, 38):

- A. The possibility of a carryover effect.
- B. The need for a long total period of treatment (extended by wash-out periods between treatments) with concomitant increases in dropouts over time and loss of statistical power. However, vigilant patient education, monitoring and follow-up may reduce dropout rates in longer trials (39).
- C. The increased likelihood of adverse events, which can unmask the blinding when a subject is exposed to both treatments.
- D. The risks for those doing well on active drug, who then may not be appropriately treated by switching to placebo. Subjects not effectively treated on active drug may not be appropriately treated by switching to placebo; and those doing

well on placebo no longer need active drug and are not appropriately treated by switching to the active drug.

- E. The subjects who respond to treatment may no longer have a diagnosis of CM, and their condition has changed within the treatment period.

*1.2.4 Randomization**Recommendations:*

Subjects should be randomized in relatively small blocks. Randomization should occur after the run-in (baseline) period. The process for maintaining randomization should be defined. The trial design should address the number of subjects needed to be randomized in order for the study to be powered adequately.

Comments:

Subjects are often recruited to prophylactic CM trials over extended periods. Therefore, it is preferable to randomize subjects in relatively small blocks to ensure balanced randomization across treatment groups.

*1.2.5 Stratification**Recommendations:*

Stratified designs may be considered within parallel group trials.

Comments:

Randomization alone does not ensure comparability among groups before treatment, and stratification for important known confounders is desirable. In trials where subjects are using acute medications frequently, the active and placebo (or sham) groups must be balanced. Consideration should be given to stratifying groups of patients who may have other prognostic factors (e.g. duration of illness).

*1.2.6 Baseline (run-in) period**Recommendations:*

A minimum of a 1-month prospective baseline period is recommended using a headache diary that captures ICHD-2 criteria for migraine without aura. Other useful diary information may include type and frequency of acute medications taken each day, headache duration, and impact of headache on the subject's quality of life. In order to confirm that a headache has been treated and relieved by a triptan or ergot (and therefore the headache meets ICHD-2, CM-R C2), there should be a reduction from moderate or severe pain to mild or no pain within 2 h after the intake of such treatments.

Comments:

Subjects need a defined baseline period in order to determine that they meet eligibility criteria for the trial and to capture data against which post-treatment effects can be measured (6, 8–20). Note that a high degree of variability in baseline frequency estimates for primary efficacy measures may diminish statistical power. Therefore, it is suggested that inclusion and exclusion criteria be carefully considered to minimize the variability of the parameter across the study population.

*1.2.7 Duration of treatment periods**Recommendations:*

A treatment period of at least 3 months is recommended. An additional long-term observational period can be considered.

Comments:

Relatively long treatment periods increase the power of the trial by providing more stable estimates of outcome measures. The efficacy of many treatments accrues gradually (i.e. some need up to 6 months before the full prophylactic potential of a medication is established). If a treatment has a rapid onset of action, and does not require dose escalation, a shorter treatment period may be appropriate. A long-term observation period may help identify additional adverse events or time to relapse.

*1.2.8 Dosage or procedures**Recommendations:*

For drug treatment trials, attempts should be made to test a wide dosage range as appropriate (e.g. minimal effective dose and maximum tolerated dose).

Comments:

As long as the basis for the efficacy of prophylactic treatment remains unknown, the choice of doses and intensity of intervention is a purely empirical compromise between observed efficacy and tolerability.

*1.2.9 Acute medication and other concomitant headache treatment**Recommendations:*

Acute treatment must be allowed. Prior to entry into the baseline period, it is important that acute treatments remain the same throughout the baseline period and for the duration of the trial. Medications with proven preventive efficacy in migraine should not be started or discontinued during the trial.

Where applicable, similar restrictions should be applied to devices and non-pharmacological treatments that have proven efficacy in migraine prevention (e.g. biofeedback), or which may reasonably be considered to alter the outcome (e.g. acupuncture, physical therapy, occipital nerve blocks).

Comments:

Acute headache medication must be allowed during the trial. Prior to the start of the baseline period, subjects should not be counselled to change their usual pattern of acute medication use. Subjects should be allowed to modify the frequency or use (e.g. to medicate their headaches) in an unrestricted manner (e.g. to increase or decrease the use of such treatments based on their own need). Any instruction on acute medication usage needs to be standardized for use across treatment centres. For example, if some subjects use acute headache medications frequently and are counselled to taper or restrict the use, this could lead to a reduction in headache frequency, duration, and/or severity and potentially confound the interpretation of prespecified outcome measures. In addition, if a subject has their acute medication changed from a simple analgesic to a triptan during the course of a trial, headache duration and intensity may be altered and potentially confound the study results.

*1.2.10 Control visits**Recommendations:*

Subjects should be followed regularly during the trial. Subjects are usually seen at the time of screening, end of baseline, and after randomization and initiation of treatment. Subsequent visits are contingent upon the treatment being tested.

Comments:

Regular subject contacts are important in order to determine eligibility, ensure compliance, and monitor for adverse events.

1.3 Evaluation of results

All primary and secondary end-points need to be defined *a priori* with specific comparative groups defined (e.g. treatment vs. placebo or vs. baseline) and time points identified (e.g. 1-month or 3-month end-points, etc.).

1.3.1 Primary end-points

The evaluation of efficacy should be based on headache diary information, which captures key assessment measures for the study. The headache diary

should be suitable for evaluating the efficacy and tolerability measures chosen from those recommended below. The details of diary design should be standardized for multinational trials, but may be translated to incorporate language and culture differences. The diary may be paper or electronic. It is important to minimize the response burden associated with diary information recording (ensuring the daily response time and burden are similar among treatment groups and regardless of headache status).

Depending on the nature of the study, there are several different end-points that may be considered as a primary end-point. Selection of the primary end-point must be done *a priori* and should depend on study objective. (For example, in studies including subjects with continuous headache, the primary end-point should not be frequency of migraine episodes, because some subjects may have a single headache that lasts for 30 days, and it will qualify as a single episode.) It is recommended that the primary end-point include headache days with moderate or severe intensity, migraine days or frequency of migraine episodes.

A. *Number of headache days with moderate or severe intensity*: A headache day with moderate or severe intensity is defined as a day with headache pain that lasts ≥ 4 h with a peak severity of moderate or severe intensity, or of any severity or duration if the subject takes and responds to a triptan or ergot. This measure allows the use of a relatively simple headache diary. Subjects indicate whether or not a headache was present (yes/no), the peak severity (mild/moderate/severe), the duration (< 4 h/ ≥ 4 h), and acute medication intake type (ergot/triptan/other). In the same diary, the subject also can indicate other headache types.*

B. *Number of migraine days*: A migraine day is defined as a day with migraine (meets ICHD-2

1.1) or probable migraine (meets ICHD-2 1.6). Subjects must:

1. have a day with headache of ≥ 4 h duration, and
2. meet criteria C and D for migraine ICHD-2 1.1 or probable migraine ICHD-2 1.6 (40), or
3. take a triptan or ergot with headache relief within 2 h.

C. *Number of migraine episodes*: In studies that include subjects who have pain-free periods, the number of migraine episodes may be considered as a primary end-point. The duration of pain-free periods between episodes must be predefined. This end-point should not be used in trials including subjects with continuous headache. A migraine episode can be defined as a headache episode meeting ICHD-2 1.1, 1.2 or 1.6.

Comments:

A headache day with moderate or severe intensity is defined as a consecutive period of time that is less than 24 hours in duration, regardless if it extends into the next calendar day for less than 4 hours. (For example, if a headache starts at 20:00 and ends at 01:00 the next morning, this will be counted as a single headache day, despite that it extends into the next calendar day for less than 4 h in duration). Number of headache days (any intensity), number of migraine days, or number of episodes (as defined above) also may be used as secondary end-points.

1.3.2 Secondary endpoints

A. *Intensity of headache*: A categorical rating scale should be used to rate each headache as mild, moderate, or severe intensity. 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 headaches that most disable subjects with CM. Depending on the trial design, subjects should be instructed to record the maximum intensity for each headache day/episode and/or each calendar day.

B. *Duration in hours*: Subjects may record the start and stop time of each headache episode. Duration alone is not recommended as an outcome measure. The duration of episodes is integrated into one of the proposed primary efficacy measures defined above (1.3.1 Number of Headache days with moderate or severe intensity). It is important to ascertain a history that the subject suffers discrete headache episodes with start

*In comparing future studies with those conducted in the past, there may be differences noted in how a 'headache day' is defined. Therefore, it is critical that each study clearly defines *a priori* what is being measured. Traditional diaries may have classified this current definition as two separate headache days, since subjects report pain on two separate calendar days. Meanwhile, other studies define a headache day as a headache of at least 30 min duration; therefore, for this new definition included herein, this would have been considered two headache days. Additionally, other studies may define a 'headache period' as the primary end-point and define it as 24 h from onset of migraine. For the above example, this would be defined as one headache period.

and stop times; between episodes they are completely pain free. Some subjects have a continuous background headache that never disappears completely, superimposed upon which they have 'episodes' that may be more severe. These subjects should not be included in clinical trials where the primary efficacy end-point is the number of migraine episodes, migraine days or headache days.

- C. *Responder rate*—number of headache days with moderate or severe intensity, number of migraine days, or number of migraine episodes: Responder rates may be included as a secondary end-point. Responder rates should be defined as either $\geq 30\%$ or $\geq 50\%$ reduction in (i) headache days with moderate or severe intensity, (ii) migraine days, or (iii) migraine episodes compared with the baseline period. Responder rates have been traditionally defined in migraine as $\geq 50\%$ reduction, but in CM population, a $\geq 30\%$ responder rate can be clinically meaningful. Other responder rates (e.g. 25%, 75%) may also be considered. However, few trials have been done that identify the optimal responder rate for use in clinical studies, and therefore the optimal responder rate is not known at this time point. Responder rates can be used in meta-analyses of placebo-controlled, randomized, controlled trials. Specific responder rates used in the trial must be defined *a priori*.
- D. *Acute treatment utilization*: Use of acute treatment should be recorded. Change in acute medication use is an important secondary outcome because it may reflect a change in headache status (positive or negative). During the baseline or trial period, subjects should not be counselled to change the type of acute treatment they normally use. Furthermore, it is recommended that subjects do not receive any special counsel to change the frequency of use of acute treatments during the treatment phase, so that any fluctuation in use (either increase or decrease) can be evaluated.
- E. *Conversion to episodic migraine*: The percentage of subjects who reduce their frequency of migraine episodes or number of migraine days may change their classification status from CM to episodic migraine. Therefore, a secondary end-point may be the percentage of subjects who convert from CM-R to a classification of episodic migraine status meeting all the ICHD-2 criteria for migraine with or without aura.
- F. *Headache index*: Headache index is defined as either (i) frequency times intensity or (ii) frequency times intensity times duration. The

disadvantage of this end-point is that performing such mathematical transformations leads to values that may not be linear. Therefore, use of headache index is not recommended as an efficacy measure specifically in acute migraine trials. Clearly, at this time the value of this end-point specifically in clinical trials in CM is relatively unexplored and requires verification before widespread use.

- G. *Subjects' preferences*: Use of subjects' preferences is not recommended as an efficacy measure. Subjects' preferences for one or another treatment can be asked only in a crossover trial. It is not recommended because it can endanger the blinding of subjects, since the design of the study has to be disclosed.

1.3.3 Healthcare outcomes/quality of life

Recommendations:

Validated disease-specific health-related quality of life and disability instruments are recommended as secondary end-points.

Comments:

Health-related quality of life (HRQOL) represents the net effect of an illness and its consequent therapy on a subject's perception of his or her ability to live a useful and fulfilling life (41, 42). HRQOL can be measured with a variety of generic and specific questionnaires. Generic questionnaires are usually chosen for comparisons between 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 CM must be scientifically developed and standardized in order to evaluate the appropriateness of HRQOL assessments and to apply the results in various clinical and research settings. Many different HRQOL instruments, combinations of HRQOL instruments, and clinical outcomes have been reported, and their use is becoming widely accepted. However, no single instrument is currently recognized as the gold standard in migraine HRQOL assessment. The future of HRQOL research may see the evolution of combined generic and disease-specific instruments. For CM there are no disease-specific instruments, but it seems likely that the migraine instruments may capture the impact of CM.

Disability measures with a 1-month recall period such as the Headache Impact Test (HIT) or the Henry Ford Disability Inventory (HDI) may be

useful. The Migraine Disability Assessment (MIDAS) questionnaire has been used in one trial (39) and proven useful; therefore, if used, the treatment period should be long relative to its 3-month recall period. A 1-month version of MIDAS is being explored. These tools may help demonstrate the humanistic benefits of treatment and help define clinically meaningful change in the context of CM-R treatment trials.

For quality of life end-points to be valid, it is also important that all instruction and education on lifestyle factors (e.g. sleep hygiene, diet, caffeine use, exercise, etc.) and other behavioural treatments (e.g. cognitive therapy, biofeedback, etc.) remain consistent among treatment groups and across centres; inclusion of any of these methods in the study design should be defined *a priori* and standardized, because they may confound study outcomes.

1.3.4 Pharmacoeconomic end-points

Recommendations:

The economic value of prophylactic treatment for CM should be assessed in studies that capture both the costs of medical treatment (direct costs) and lost productive time (indirect costs).

Comments:

The high cost of CM to individual sufferers and society may be offset or reduced by effective prophylaxis treatment. The costs of medical treatment can be estimated using diaries or electronic data before and after treatment. Lost productive time (e.g. work, household works, other activities) can be measured (i) using self-reported diaries, (ii) through experience-based sampling, or (iii) by the use of employer work records. To demonstrate that treatment for CM is both effective and cost-effective would support the development of health policies that make CM a priority.

1.3.5 Adverse events

Recommendations:

Adverse events (AEs) during treatment should be standardized, and methods to do this include spontaneous reports recordings, open-ended questions, and direct questioning. Details on reporting AEs should be recorded according to local IRBs, regulatory authority guidelines, and Good Clinical Practice Guidelines (42, 43)

Comments:

AEs tend to occur before maximum efficacy, and in clinical practice AEs are a major problem in prophylactic migraine treatment, often leading to

discontinuation of treatment. Incidence of AEs, especially those leading to discontinuation of treatment, should be regarded as one of the major measures of the tolerability and safety of a prophylactic migraine treatment.

AEs, or unwanted effects that occur during treatment (14), are not necessarily related to treatment. They should be recorded openly in order to detect any unexpected unwanted effects during the development programme of a drug. Investigators can indicate whether they believe that the AE is treatment related. It should be noted that regulatory authorities require more detailed reporting of AEs with new experimental treatments (42, 43).

1.4 Statistics

In preplanning the analysis of data for CM studies, a primary measurement time to determine study outcome should be defined *a priori*. A primary efficacy variable should also be defined *a priori*. Consideration should be given regarding how to collect accurate data to evaluate a change in efficacy variables. For instance, if headache frequency is to be evaluated, then record of occurrence, start and stop times, duration of headache episodes, and minimum duration required for counting the headache episode (e.g. ≥ 4 h) are all individual outcomes that should be explored and defined *a priori*. Target sample size needed to achieve appropriate power for statistical significance among treatment groups needs to be defined *a priori*. Comparisons between the treatment phase and baseline phase need to be specifically defined *a priori* as primary or secondary end-points, or both.

Consideration also should be given to the rules of estimation for missing data for designated variables. For example, if the headache stop time is to be captured and it is unknown, a decision rule might be to assume that the headache stopped at the end of the last day (e.g. 23.59 h) that it was reported to be ongoing. Such decision rules should also be defined *a priori*. 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.

Methodology for comparisons between treatment groups should be defined *a priori*. The analysis population should be clearly defined. In general, the subjects should be analysed according to the randomization assignment, regardless of actual treatment received (intent-to-treat population, analysed as randomized). For safety variables, it

might be reasonable instead to analyse the subjects according to the treatment the subject actually received (safety population, analysed as treated).

In order to have data for all subjects in the intent-to-treat population, one could impute missing data for at least the primary variable of interest, either as a primary analysis or as a sensitivity analysis. Alternate statistical analysis may be used if verified by a statistician.

1.5 Publication of results

Prior to initiation of the study, registration of the trial is necessary for publication in some peer-reviewed journals. Publication (preferably in manuscript form) of all research results (primary and secondary end-points and all safety data) is necessary. This Subcommittee therefore strongly supports one of the firm recommendations of the Ethics Subcommittee of IHS (22):

'As a general rule, every methodologically sound randomized controlled trial should be published (and only such trials should be carried out). Publication should be in such a way as to allow evaluation of the results; publication solely as an abstract or in non-peer-reviewed supplements is unacceptable.'

Investigators and sponsors should negotiate time-lines for publication at the onset, and ideally they should form part of the protocol. A publication committee should be formed prior to the start of the study.

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Appendix I

Summary table: guidelines for controlled trials of prophylactic treatment of chronic migraine in adults

1. Drug trials dealing with chronic migraine prophylaxis	
1.1 Selection of subjects	
1.1.1 Chronic migraine definition	Use diagnostic criteria of appendix ICDH-2 for CM-R (A1.5.1) [3]
1.1.1.1 Chronic migraine with MOH	Subjects meeting the criteria A to C but not the criterion D of CM-R (i.e. MOH-R are also met) may be included in the trials for CM [3]; however, subjects with MOH-R must be stratified accordingly.
1.1.2 Other (non-migrainous) headaches	Permitted if well-recognized by the subject
1.1.3 Duration of disease	> 6 months
1.1.4 Duration of observation	3 months retrospective and 1 month prospective recording with a detailed headache diary
1.1.5 Age at onset	< 60 years
1.1.6 Age at entry	≥ 18 years
1.1.7 Enrolment	Clear explanation of trial purpose
1.1.8 Gender	Both female and male subjects
1.1.9 Coexistent disorders	Screen and treat for prevalent coexisting conditions (e.g. depression)
1.1.10 Concomitant drug use	Studies of monotherapy are recommended; adequate wash-out periods required to ensure no carry-over effect after discontinuation of other medications or treatments (> 1 month in crossover trials)
1.2 Trial design	
1.2.1 Blinding	Use double-blind technique
1.2.2 Placebo control	Recommended, see text

Appendix I (Continued)

1.2.3 Parallel-groups and crossover designs	Use parallel-group comparison. For comment on crossover design, see text
1.2.4 Randomization	Randomize in small blocks
1.2.5 Stratification	Can be used, if possible, in parallel group comparison
1.2.6 Baseline (run-in) period	At least 1 month in duration
1.2.7 Duration of treatment periods	At least 3 months
1.2.8 Dosage or procedures	Use as wide a range of doses as possible to establish minimal effect and maximum tolerated dose
1.2.9 Acute medication and other concomitant headache treatment	Keep usual treatment constant during the trial
1.2.10 Control visits	Screening, end of baseline, and every 4-6 weeks after randomization and initiation of treatment
1.2.11 Subjects who have already participated in previous headache trials	Not recommended for a trial of similar treatment
1.3 Evaluation of results	
1.3.1. Primary end-point	Must be defined <i>a priori</i>
1.3.1.A Number of headache days (with moderate to severe intensity)	Number of days with headache pain that lasts ≥ 4 h on a calendar day and has a peak severity of moderate or severe pain, or of any severity if the subject takes a triptan or ergot
1.3.1.B Number of migraine days	The number of days with migraine or probable migraine (meets ICHD-2 1.1; 1.2, 1.6). Subjects must have a headache that lasts ≥ 4 h on a calendar day, meets criteria C and D for migraine ICHD-2 1.1, 1.2, or 1.6 [40], or take a triptan or ergot
1.3.1.C Number of migraine episodes	In studies including subjects who have pain-free periods, the duration of pain-free periods between episodes must be predefined. This end-point should not be used in trials including subjects with continuous headache. A migraine episode is defined as a headache episode meeting ICHD-2 1.1, 1.2 or 1.6 [40]
1.3.2. Secondary end-points	
1.3.2.A Headache intensity	A categorical rating scale should be used to rate each headache as mild, moderate, or severe intensity; see text
1.3.2.B Duration in hours	Subjects may record the start and stop time of each headache episode; see text
1.3.2.C Responder rate for headache days with moderate or severe intensity, migraine days, or migraine episodes	Responder rates should be defined <i>a priori</i> and most often include $\geq 30\%$ or $\geq 50\%$ reduction in (i) headache days with moderate or severe intensity, (ii) migraine days, or (iii) migraine episodes vs. baseline. Other responder rates (e.g. 25%, 75%) may also be considered
1.3.2.D Acute treatment utilization	Change in acute medication use is an important secondary outcome (subjects should not be counselled to change the type of acute medication or frequency of use during the trial)
1.3.2.E Conversion to episodic migraine	The percentage of subjects with a reduction in migraine days (e.g. % who convert from CM-R to episodic migraine) to < 15 days/month
1.3.2.F Headache index	A headache index is defined as headache duration times the headache severity times the number of days. The value of this end-point specifically in clinical trials in CM is relatively unexplored, but may be considered as a secondary end-point
1.3.2.G Subjects' preference	Not recommended as may be unblinded in crossover trials or with AEs
1.3.3 Healthcare outcomes/quality of life	Validated disease-specific health-related quality of life and disability instruments as secondary end-points
1.3.4 Pharmacoeconomic end-points	The economic value should be assessed using costs of medical treatment (direct costs) and lost productive time (indirect costs)
1.3.5 Adverse events	Should be recorded, see text
1.4 Statistics	Analysis plan must be defined <i>a priori</i>
1.5 Publication	All safety and efficacy results must be published and made available for review