

Guidelines for controlled trials of drugs in migraine: second edition

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Introduction

In 1991 the Clinical Trials Subcommittee of the International Headache Society (IHS) published its first edition of the guidelines on controlled trials of drugs in migraine (1). The guidelines were developed because of a need 'to improve the quality of controlled clinical trials in migraine', and because only quality trials can form the basis for international collaboration on drug therapy. Their main purpose was to draw the investigators'

attention to the problems inherent in drug trials in migraine. More recently, the committee has published similar guidelines for tension-type headache (2) and for cluster headache (3).

Since then, the extensive trial programme for sumatriptan adopted methods in some ways different from those we recommended (4, 5, 6, 7), and recent and current trials with other new 5-HT_{1B/1D} receptor agonists (triptans) are using similar methods (8, 9, 10, 11, 12, 13, 14). The experience of clinical investigators and the pharmaceutical industry has expanded enormously, providing a basis for revising these guidelines now.

With the current trend for huge multinational trials there is a need for increased awareness amongst clinical investigators of methodological issues in clinical trials of drugs in migraine. These guidelines deal with those specific for this illness.

For discussion of issues applying to clinical trials in general the reader should consult general works on clinical trial methodology (15, 16, 17, 18). There are a number of sources of previous discussions on these issues (19, 20, 21, 22, 23, 24, 25, 26).

Migraine is treated with drugs for the acute attack, with prophylactic drugs, or both. Naturally, trials of these two types of migraine therapy have different designs. Accordingly the guidelines have separate sections for each, comprising the following subsections: patient selection, trial design, evaluation of results, and statistics. At the end checklists for both acute and prophylactic trials treatments are given. In addition, short-term prophylaxis is sometimes used to prevent predictable migraine attacks, such as those associated with menses (27), and trials of such treatments introduce particular demands (see special comments, section 3.5).

Suggestions on the various points are given, but only a few are firm recommendations, and none should be regarded as dogma. The subcommittee believes, and the comments sections indicate, that various solutions to specific problems can be equally appropriate.

For ethical issues in migraine research and management, separate guidelines have been published (28).

1. Drug trials dealing with the treatment of the migraine attack

In trials dealing with the treatment of the migraine attack investigators should be aware that the headache is not a stable pain but develops gradually, or sometimes rapidly, to a peak with subsequent spontaneous resolution. This poses challenges regarding timing of intake of test medication, which might be early or when the attack is fully developed, and in evaluation of results. In migraine with aura there is the option for treatment during the aura phase in an attempt to protect against the development of headache. This option has been the subject of special placebo-controlled trials (29, 30). Additionally, within subjects there is a high level of variability from attack to attack (31, 32).

1.1 Selection of patients

1.1.1 Migraine definition

Recommendations: The diagnostic criteria should conform to those of the IHS (*Cephalalgia* 1988; 8(Suppl 7):1–96, with an expected revision in 2001).

Comments: Diagnostic criteria of the IHS should be adhered to strictly. There are people with attacks that do not meet IHS criteria but, nevertheless, are diagnosed with migraine and respond to migraine therapy. For clinical drug trials, however, requirements are more rigid than in clinical practice. Relatively few people will be excluded by requiring IHS criteria.

The IHS diagnostic criteria classify attacks, and some patients have in their life times attacks both with and without aura. Thus some patients can be classified as having migraine with aura and migraine without aura. If patients are to enter a trial specifically concerning migraine with aura, investigators might arbitrarily require that more than 90% of attacks were with aura during the last 2 years to enhance the probability that the treated attack(s) would be with aura. Similarly, more than 90% of attacks for migraine without aura in over 2 years might be requested in trials concerning migraine without aura (although patients with exclusively migraine without aura are more easily found). Theoretically, during the trial each attack should be classified according to the IHS criteria according to clinical

features captured on a diary card. However, these features may be modified by treatment so this may be a meaningless requirement.

Regarding the separation of migraine without aura and tension-type headache, consult the IHS criteria (33).

1.1.2 Other (non-migrainous) headaches

Recommendations: Other headaches are permitted if the patient can differentiate them from migraine by the quality of pain (one-sided, pulsating, moderate or severe intensity), or by the profile of associated symptoms (i.e. nausea, discomfort to light or sound, visual symptoms or other aura), or both.

Early safety and efficacy studies should exclude other headache.

Comments: Many patients with migraine have so-called interval headaches which do not meet IHS criteria for migraine (*Cephalalgia* 1988; 8(Suppl 7):1–96). Future studies may show that interval headaches are indeed fragments of migraine without aura but, for the present, patients who cannot distinguish interval or other, non-migrainous headaches from typical migraine without aura must be excluded.

1.1.3 Frequency of attacks

Recommendations: Attacks of migraine should occur one-six times per month. The frequency of other (including interval) headaches should be no more than 6 days per month. There should be at least 48 h of freedom from headache between attacks of migraine.

Comments: In order to avoid very long trials a minimum of one attack per month is recommended. The maximum frequency of six per month is not absolute and allows for more rigid standards in certain trials. Other headaches of more than 6 days per month may blend into attacks of migraine without aura if migraine were also to occur as often as six per month. Forty-eight hours of freedom between attacks of migraine permits identification of individual attacks, distinction from relapse (recurrence), and avoids multiple treatments within one prolonged attack.

1.1.4 Duration of disease

Recommendations: Migraine should have been present for at least 1 year.

Comments: Because there are no objective signs of migraine, a minimum course of 1 year is advisable to help exclude other types of headaches which may mimic migraine. At least five prior attacks of migraine without aura or two prior attacks of migraine with aura are essential for diagnosis by the IHS criteria (33).

1.1.5 Duration of observation

Recommendations: There should be a 3-month well-documented retrospective history or 1-month prospective baseline recording.

Comments: Prospective observation is generally not essential in drug trials evaluating acute treatment for migraine, although it may be desirable in trials involving aura or pre-emptive treatment strategies.

1.1.6 Age at onset

Recommendations: The age at onset of migraine should be less than 50 years.

Comments: Migraine beginning after the age of 50 is rare (<2%) and headache onset in these years is often due to underlying organic disease that sometimes mimics migraine. Few patients will be excluded by this limitation.

1.1.7 Age at entry

Recommendations: Patients may be entered into adult studies between 18 and 65 years of age.

Comments: Drug development programmes may at some point wish to include both younger and older patients. Special protocols will be required for children and adolescents (under the age of 18) (34) in order to show efficacy as well as safety (see 3.4). Migraine attacks are often short-lasting in children, and placebo-response is high (see special comments). Special protocols are also needed for migraineurs over the age of 65. Because they are subject to cerebrovascular disease and other illnesses that increase the hazard in using experimental drugs, elderly patients should not be included until safety has been shown in younger adults.

1.1.8 Gender

Recommendations: Both male and female patients are acceptable.

Comments: There are more women than men in the migraine population. In most migraine trials, however, this female preponderance is exaggerated. Efforts should be made therefore to recruit males to an extent that reflects its epidemiological prevalence (35, 36, 37, 38).

In studies of women precautions should be taken to avoid treating women who may be pregnant or lactating unless this is the purpose of the study.

Menstrual migraine is discussed in section 3.5.

1.1.9 Concomitant drug use

Recommendations: Other concomitant therapy, specifically allowed or restricted, should be specified. In very early trials of safety and efficacy, the patient should not take other drugs. In later trials contraceptive drugs,

drugs used for migraine prophylaxis and other drugs not taken for migraine that may alter metabolism of or are otherwise likely to interact with the experimental drug may be specifically permitted with due precautions. Withdrawal of prophylactic drugs prior to entry, if they are excluded, should be completed at least 1 month beforehand. When they are permitted, patients recruited on prophylaxis should have been on stable doses (for at least 3 months) of no more than one prophylactic agent.

Excluded are the following: patients who use drugs excessively for headache (for example, those who regularly take medication for acute headache on more than 10 days per month); patients who have taken antipsychotics, or antidepressant medications (unless only for migraine prophylaxis), during the previous 3 months; patients who abuse alcohol or other drugs (DSM-IV criteria (39)); patients who are allergic or have shown hypersensitivity to compounds similar to the trial drug; potentially fertile and sexually active women who do not practise an acceptable form of contraception.

Comments: Evaluating potential for drug interaction is an important aspect of drug development prior to marketing. In these recommendations, safety of participants is the primary concern, but drug interaction may also obscure treatment effect or its measurement.

To exclude patients who occasionally use a sedative or minor tranquilizer is not sensible in later trials, nor is exclusion of women who experience no difficulty using contraceptive drugs. Both would too severely limit the population from which recruits may be drawn, and these are groups of patients who will seek to use a marketed acute migraine therapy. On the other hand, it is desirable to eliminate patients who take excessive drugs for the treatment of acute headache, because pathophysiology and response to treatment are likely to be altered, and those who abuse drugs or alcohol. People who are known to be resistant generally to anti-migraine drugs may unfairly bias the study if preferentially selected, which may happen because of their availability unless they are excluded. However, unresponsiveness to medication may be due to inadequate dose, short duration of trial or other factors. These patients are not unequivocally excluded, but investigators should set clear criteria for their inclusion in the protocol. It should be noted that many patients consider headache recurrence as a failure despite experiencing initial relief, and these should be distinguished.

1.2 Trial design

1.2.1 Blinding

Recommendations: Controlled trials concerning acute treatment should be double blind.

Comments: Drugs used for acute treatment of migraine can be reliably evaluated only in randomized, double-blind, clinical trials.

Clinical observations, most likely with drugs primarily used for other indications, may, however, be the impetus for conducting randomized clinical trials.

1.2.2 Placebo control

Recommendations: Drugs used for the acute treatment of migraine should be compared with placebo.

When two presumably active drugs are compared, placebo control should also be included in order to test the reactivity of the patient sample.

Comments: The placebo effect in the treatment of migraine attacks varies from 6% (40) to 47% (41) for headache relief. Active drugs should therefore be demonstrated to be superior to placebo. Demonstration that a standard drug and a novel comparator agent do not significantly differ in a trial does not prove that the novel agent is effective (42). Referring to historical controls for the active comparator is not a substitute for a contemporaneous placebo-control group.

1.2.3 Parallel-groups and crossover designs

Recommendations: Both parallel-groups and crossover designs can be used.

Comments: The parallel-groups design has the advantage of simplicity. Parallel-groups studies have successfully demonstrated both superiority and comparability among drugs (14, 43, 44). With a crossover design a period effect may occur although there is probably no risk of carryover effect in acute treatment trials. The crossover design allows robust estimates of intraindividual consistency of response using placebo-control groups (e.g. (45)). In addition, it allows assessments by the patients of the benefit/tolerability ratio by asking for their preference of two or more active drugs or doses (46).

1.2.4 Randomization

Recommendations: Patients should be randomized both in crossover and parallel-groups trials.

Randomization should occur at entry to the trial.

Comments: True randomization is crucial to avoid bias and, in large trials, contribute to group matching. In acute treatment trials there is no reason to delay randomization once a patient is selected for entry.

1.2.5 Stratification

Recommendations: In general, there is no need for stratification in acute treatment trials.

Comments: Randomization alone does not ensure comparability between patients in the different treatment

groups, and stratification for the most important prognostic factors should ideally be used. Such factors are not well recognized. Migraines with and without aura appear to respond similarly to medication (e.g. (5)). Age and body weight have been shown to predict treatment response in selected studies (47, D Gutterman, personal communication). Intensity of headache at the time of treatment is predictive for outcome with a number of treatments (48, Tfelt-Hansen, personal communication); stratification for this variable is possible in studies conducted in inpatients, but probably not otherwise.

1.2.6 Dose-response curves and dosage

Recommendations: (a) In assessing a new drug for acute migraine treatment the dose-response curve should be defined in randomized, clinical trials. The minimum effective dose and the optimum dose(s) (based on both efficacy and tolerability) should be determined. (b) In comparative randomized clinical trials, appropriate doses of each drug should be used. If these are not the clinically recommended dose(s), explanation must be given.

Comments: Dose-response curves have been established for many triptans (8, 9, 10, 11, 12, 13, 14). The optimal doses for each triptan are reasonably well established. When a dose-range for an established comparator drug is given, then a range of doses for the new drug should be evaluated against this dose-range.

For drugs primarily developed for other diseases, no dose-response curves for their efficacy in migraine have been established so far, and the dosage used in clinical trials in migraine will normally be the dosage used for other pain states.

1.2.7 Route of administration

Recommendations: (a) In early (Phase II) trials to establish efficacy (proof of concept) parenteral therapy, if possible, is preferable. (b) Oral administration, a mode of administration preferred by most patients, for a new drug can be used if kinetic data indicate a quick absorption and adequate bioavailability. (c) Alternative routes, especially in severely nauseated patients, include the injected, inhaled, sublingual, intranasal and rectal routes.

Comments: In early Phase II clinical trials, parenteral administration will optimize drug delivery; negative results cannot be attributed to poor oral absorption. Investigators should be aware that oral absorption of drugs is often delayed during migraine attacks (49, 50, 51, 52). Ideally, oral agents should be investigated kinetically both during and outside migraine attacks, to establish an appropriate pharmacokinetic profile before embarking on a controlled trial.

1.2.8 Time of administration

Recommendations: Study designs should time dosing to address drug administration either early in the attack or after the attack is fully developed.

Comments: In principle, treatment should be started as early as possible during the headaches phase to mimic clinical practice. However, in migraine without aura the patients may have difficulties in distinguishing between this and interval or other headache in the beginning of an attack, and may consequently treat other headaches. Fully developed attacks are easily distinguished from interval headaches. In addition, waiting until the headache is moderate or severe may increase the sensitivity of migraine as a pain model. On the other hand, some drugs may be more effective when taken early. Preferably, a drug should be investigated both as early treatment and as treatment for fully developed attacks such as early morning migraine (53).

1.2.9 Number of attacks treated with same treatment

Recommendations: In crossover and parallel-groups trials, one attack may be treated with the same drug.

Comments: Repeated intake of the test drug was previously used and recommended (1) as it may be expected to increase the discriminative power of a trial if outcome is averaged across multiple attacks for each patient. However, repeated intake of test medication prolongs the trial considerably, especially in crossover trials, and patients often fail to treat all attacks if they are expected to treat more than four–six attacks (54, 55). Drop-outs may be related to previous lack of efficacy, thereby causing bias. The increase in power expected from repeated intake is therefore often more than counterbalanced by the decrease in number of patients completing the trial. Furthermore, repeated intake of placebo should be limited.

Finally, repeated intake (e.g. three times the same doses) has been used to evaluate consistency of response in some randomized, clinical trials (RCTs) (4, 56). Consistency of response is, however, better evaluated in specially designed RCTs (see 1.2.11).

1.2.10 Rescue medication

Recommendations: Rescue medication should be allowed after 2 h.

Comments: In some cases with parenteral drug administration rescue medication could be used after, e.g. 60 min, but in most cases with oral administration it is preferable to wait 2 h before rescue medication is allowed. Rescue medication should not be delayed more than 2 h: if rescue is needed then, the trial treatment is

unsatisfactory and not a lot is learned by delaying rescue and extending the patient's discomfort.

1.2.11 Randomized clinical trials (RCTs) evaluating consistency of response (pain-free within 2 h)

Recommendations: Consistency of response should be evaluated in modified-design crossover RCTs with placebo-control. The optimal number of attacks for such consistency trials is five and, in a double-blind design, four are treated with active medication and each of the first to fifth, in five treatment groups, with placebo.

Comments: Consistency of response for headache relief has been claimed in long-term studies intended primarily to assess long-term safety. These studies are not placebo-controlled and patients in these studies are selected based on prior response to the drug. Five attacks in a consistency RCT is recommended as a practical compromise. Investigators can either include one placebo treatment for all patients, the design recommended above or, in one group, administer active drug in all attacks. The number of attacks treated with active drug can thus be either four or five. A similar design with four attacks treated has been used in one trial evaluating consistency for headache relief (45).

With the relatively few attacks that can be treated in placebo-controlled RCTs development of tolerance to the drug (tachyphylaxis) cannot be evaluated.

1.3 Evaluation of results

1.3.1 Attack report form (diary)

Recommendations: A simple report form suitable to answer the main objectives of the trial should be used.

Comments: Quantity and quality of collected data tend to vary in inverse proportion. Complicated report forms with detailed description of symptoms of the actual attack may be difficult for patients to fill out during migraine attacks. Algorithms to ensure that the treated attack is a migraine attack have been used successfully, e.g. (57, 58).

For purpose of familiarization, patients may complete the diary whilst treating one attack with their usual treatment before inclusion in a trial, or they complete the diary at the randomization visit recalling their most recent attack. Probably the latter procedure is more acceptable for the patient expecting to try a new trial drug as soon as possible.

1.3.2. Percentage of patients pain-free at 2 h

Recommendations: Percentage of patients pain-free at 2 h, before any rescue medication, should usually be the primary measure of efficacy.

Comments: This measure is clinically relevant, reflects patients' expectations (59, 60), is simple and not affected by rescue medication (allowed after 2 h (1.2.10)). It can be used in migraine attacks with aura as well as without aura. Resolution, not alleviation, within 2 h might seem unrealistic with some drugs. It is, however, difficult to choose a longer time than 2 h, because, for practical and ethical reasons, patients should be allowed to take their rescue medication after no more than 2 h. This measure is suggested as the primary but not the only one for efficacy.

If a drug is rapidly effective (i.e. if parenterally administered) time points earlier than 2 h may be selected.

In the trial programmes for many triptans, the primary endpoint was headache relief (also called headache response), not pain free (see 1.3.5). Using headache relief a success is defined as a decrease in headache intensity from severe or moderate to mild or none (4, 8, 9, 10, 11, 14). This criterion was based in part on the clinical experience that a patient can state that the migraine attack is 'cured' whilst some residual headache may persist (4). However, this criterion treats a change from severe pain to no pain and a change from moderate pain to mild pain as equivalent (48). Furthermore, patients do not consider a decrease from moderate to mild headache a successful treatment (61); rather, surveys of migraine sufferers indicate that they wish, and expect of a treatment, to be pain free (59, 60). Therefore, whilst headache relief is statistically more powerful than the IHS recommended criterion (62) for separating active drugs from placebo, it cannot be considered clinically appropriate.

1.3.3 Sustained pain-free

Recommendations: Sustained pain-free is defined as pain-free within 2 h with no use of rescue medication or relapse (recurrence) within 48 h.

Comments: This is the ideal response to a drug for treatment of a migraine attack and should be the final goal in drug development. In addition, it deals with the problem of comparing recurrence rates among different drugs (63). With current drugs sustained pain-free as defined is probably obtained only in 15–25% of attacks treated. It will probably be useful in discriminating between triptans, but the low percentages of success measured by this criterion do not reflect the enormous clinical impact of the triptans on migraine treatment. Currently, sustained pain-free should be used as a secondary efficacy measure.

1.3.4 Intensity of headache

Recommendations: (a) The intensity of headache should be noted by the patient just before the drug intake and

up to 2 h later, before any rescue medication, on a verbal scale: 0 = no headache; 1 = mild headache; 2 = moderate headache; 3 = severe headache. (b) Alternatively, visual analogue scales can be used.

Comments: This verbal/numerical scale is simple and has been used successfully in RCTs for acute migraine treatment for many years. Visual analogue scales are probably most suitable for trials that include patients with mild and moderate headache.

Pain Intensity Difference (PID) and Sum of Pain Intensity Differences (SPID), widely used in other pain models (64, 65), have not been widely used in RCTs concerning the acute treatment of migraine. SPID, based on the above verbal/numerical headache intensity scale (0–4), could theoretically be useful since it has the advantage of summarizing the benefits of treatment over a clinically relevant period, e.g. 2 h. PID assumes that the pain scale is linear and that a change from severe to moderate headache is equivalent to a change from moderate to mild headache. This has not been analysed so far and the use of PID and SPID in migraine RCTs will have to await such analysis.

1.3.5 Percentage of patients with a decrease in headache from severe or moderate to mild or none within 2 h: 'headache relief'

Recommendations: Percentage of patients with a decrease in headache from severe or moderate to none or mild within 2 h, before any rescue medication, should be used as a secondary efficacy measure. With parental administration a drug may be quickly effective and the time point for 'relief' of the attack can be less than 2 h.

Comments: Headache relief (also called headache response (4)) should still be used, mainly to facilitate comparison of results in new randomized clinical trials (RCTs) with those of previous trial programmes for the triptans (6, 7, 8, 9, 10, 11, 12, 44).

For the short-comings of this measure, see comments on 1.3.2.

1.3.6 Time to meaningful relief

Recommendations: Time to meaningful relief can be used as a secondary efficacy measure.

Comments: Meaningful relief is usually defined subjectively by the patient. In general, patients measure time to meaningful relief using a stop watch (66). This method improves the precision of time estimates over fixed interval assessments commonly used in migraine trials.

A strength of this method is that it captures and summarizes information about treatment response, not at a pre-specified point in time (i.e. 2 h) but over a clinically relevant period of time. This dichotomous endpoint can be analysed using powerful statistical

methods such as survival analysis (66, 67). In a variant of this method meaningful relief can be assessed at fixed intervals, but this advantage is then lost.

1.3.7 Duration of attacks

Recommendations: Duration of attacks should not be used as an efficacy measure.

Comments: With the now proposed efficacy measure, percentage of patients pain-free at 2 h, and sustained pain-free, there is no need for duration of attacks as an additional measure. Time of onset and offset of symptoms, including headache, are not always easily determined, especially when the patient sleeps. Furthermore, rescue medication, allowed after 2 h, may heavily influence duration of attacks, thus invalidating this measure.

1.3.8 Speed of onset of action

Recommendations: Speed of onset of action can be evaluated by comparing the drug with placebo at earlier time points than 2 h.

To compare the speed of onset of two active drugs time-to-event analysis can be used.

Comments: Depending on the route of administration patients can be asked to rate their headache intensity at several time points from 10, 15 and 30 min up to 2 h, although this procedure may complicate the headache diary. Standard statistical analysis can then determine when a significantly superior effect compared with placebo is present. The difference to placebo should be given as the percentage with 95% CI. So far these early responses are of a relatively small magnitude except for subcutaneous sumatriptan (14, 67).

To compare the speed of onset of two active drugs, time-to-headache response analysis has been suggested and used (68, 69). In future RCTs, time-to-pain-free (e.g. (70)) should be the focus of time-to-event analysis.

1.3.9 Rescue medication

Recommendations: The use of rescue medication 2 h (or earlier) after the intake of the test drug can be used as an efficacy measure.

Comments: This measure correlates well with the patient's judgement of the efficacy of the test drug. It is, however, less sensitive than the main measure, pain-free within 2 h. In addition, the use of rescue medication probably depends on what the trial and rescue drugs are. Some patients will not take an analgesic if a triptan has had no effect after 2 h but will if pain has almost gone. If the rescue medication is a triptan, the effect may be quite different. Furthermore, patients may rescue for reasons unrelated to the pain response, such as anxiety or habit.

1.3.10 Global evaluation of medication

Recommendations: A simple verbal scale should be used by the patient: very poor, poor, no opinion, good, very good. Such scales should always be symmetrical about the neutral point.

Comments: This criterion may be one of most clinically relevant, as it takes into account both efficacy (on headache and associated symptoms) and tolerability; the latter excluding its use as the primary efficacy measure. It is probably best used in later trials. It is also useful for comparing active medications. Several reasonable scales have been used (e.g. 71, 72).

1.3.11 Functional disability

Recommendations: Functional disability should be noted by the patient just before the drug intake and up to 2 h later, before any rescue medication, on a categorical verbal/numerical scale:

0: No disability: able to function normally.

1: Performance of daily activities mildly impaired: can still do everything but with difficulties.

2: Performance of daily activities moderately impaired: unable to do some things.

3: Performance of daily activities severely impaired: cannot do all or most things, bed rest may be necessary.

Comments: This scale measures the level of impairment to the patient's daily activities and is thus an important efficacy measure. It takes into account the impact of both headache and associated symptoms on the patient (and adverse effects of medication). It can be used as a secondary efficacy measure.

1.3.12 Presence of nausea and/or vomiting

Recommendations: The presence of nausea and/or vomiting should be recorded at time of intake of test medication and after 2 h.

Comments: Nausea and vomiting are important associated symptoms of the migraine attacks (33) and drugs used for migraine treatment should also be demonstrated to be effective against these symptoms. They can occur also as adverse effects of test medication and should therefore be noted at least up to 24 h; however, after 2 h the occurrence of nausea/vomiting may be due to rescue medication.

In special trials evaluating antiemetics or combinations with antiemetics, nausea can be rated on a 4-point categorical verbal/numerical scale (0=none, 1=mild, 2=moderate, or 3=severe) and this scale has been used in a diagnostic headache diary (31) and in two RCTs (43, 73).

1.3.13 Presence of photophobia and phonophobia

Recommendations: The presence of photophobia and phonophobia should be separately recorded at time of intake of test medication and after 2 h.

Comments: Photophobia and phonophobia are often bothersome associated symptoms of migraine attacks and drugs used for migraine treatment should also be demonstrated to be effective against these symptoms. They can be rated as present or absent or on a 4-point verbal intensity scale (73).

1.3.14 Adverse events

Recommendations: Adverse events during treatment should be recorded contemporaneously in the study diary. Spontaneous reports supplemented by response to open questions are recommended. Adverse events should be rated as mild, moderate, or severe; serious or non-serious; and the time of occurrence and duration should be noted. Serious adverse events have to be handled according to GCP guidelines (74, 75).

Comments: Adverse events, unwanted effects that occur during treatment (18), 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 adverse event was drug-related. It should be noted that regulatory authorities require more detailed reporting of adverse events with new drugs (74, 75).

1.3.15 Patients' preferences for treatments

Recommendations: Patients' preferences for treatments can be used in crossover trials.

Comments: Benefit/tolerability ratios are difficult to judge from currently performed RCTs. It is unknown how a certain success rate and an incidence of adverse events should be combined into a meaningful expression for the benefit/tolerability ratio. Many patients seem to prefer a more effective drug or dose and will endure the cost of more adverse events if these are relatively transient and mild (14, 44). In crossover RCTs patients can assess the benefit/tolerability ratios of different drugs or doses by giving their preference for different treatments (e.g. (46)). Preference has not been asked in some recent crossover RCTs (69, 76).

1.3.16 Incidence of relapse (recurrence)

Recommendations: Relapse occurs when a patient is pain-free within 2 h after treatment and headache of any severity returns within 48 h. This represents secondary treatment failure. The incidence of relapse and time to relapse should be recorded for the different treatments

in the trial and reported as the percentages of initial responders.

Comments: Previously the term *recurrence* has been used. In most trials this has been defined as worsening of headache (to moderate or severe pain) within 24 h of treatment and subsequent to headache response (mild or no pain) (44). It has been suggested that headache response and absence of recurrence might be termed *sustained response* (77). The change in terminology to *relapse* is advised because of the change in definition (to avoid confusion), and also because *relapse* better describes return of symptoms following their abolition by treatment. With the presently suggested primary efficacy measure, pain-free within 2 h, relapse is simpler for patients to record than recurrence as previously defined.

Relapse and recurrence are a major problem with all effective migraine treatments (14, 44) and should be recorded as an important efficacy index. The reported incidence of recurrence as previously defined varies considerably, e.g. from 6% to 44% of initial responders for oral sumatriptan (14), and will most likely vary similarly with the presently suggested definition of relapse. Comparison of relapse/recurrence rates for different drugs can thus be based only on comparative RCTs, although it has been suggested that comparison of recurrence rates is only possible when primary efficacy rates are comparable (63). A composite measure which integrates initial response, no use of escape medication and no relapse (63, 78) may solve these problems. Such a measure is the suggested *sustained pain-free* (see 1.3.3).

Specially designed RCTs are needed to evaluate relapse/recurrence beyond 48 h in patients with multiple recurrences, in some cases over several days with repeated treatment intake (63).

1.3.17 Treatment of relapse

Recommendations: The efficacy measure for treatment of headache relapse should be the percentage of patients pain-free within 2 h of taking the treatment for it.

Comments: Relapse of any severity of headache can be treated with active drugs or placebo in a randomised double-blind clinical trial. So far, the efficacy of the triptans on recurrent headaches are in the same range as the primary effect on the headache as judged by the headache relief criterion (14).

1.3.18 Consistency of effect (pain-free within 2 h)

Recommendations: In special crossover design trials comparing active drug and placebo, consistency can be defined as treatment success (preferably defined as pain-free within 2 h) in at least three of four attacks consecutively treated with active drug (see 1.2.11).

Comments: In RCTs comparing active drug and placebo two types of multiple attack measures may be reported. Intra-individual consistency (defined above) is the percentage of individuals in a group who respond in a specific number out of a larger number of treated attacks (e.g., three out of four). Population consistency, which may also be of interest, is the proportion of a group who respond in their first, second or nth treated attack.

Depending on the design in these RCTs four or five attacks are treated consecutively with the same dose of a drug (see 1.2.11) and consistency, defined as above (or as four out of five), can be reported. So far, consistency of response (for headache relief) has been evaluated only in a few RCTs (e.g. 45, 71, 79).

1.4 Statistics

The recommended primary efficacy measure for single attack studies is the percentage of patients who are pain-free within 2 h of taking study medication. Inferences regarding differences can be assessed using standard statistical methods. To calculate sample size, the investigator needs to estimate the placebo response and define the clinically significant difference to be detected.

Standard statistical methods can also be used for analysis of assessment measures in both crossover and parallel-group trials. A period effect has been found in some crossover trials and should be dealt with appropriately. Confidence intervals for differences between an active drug and placebo and between two active drugs (14, 44, 67, 80) are recommended in order to inform the reader more fully of the meaning of the results of the trial. A statement that two drugs are comparable without giving confidence intervals is unacceptable.

Time-to-event (pain-free) analysis (68) or time-to-meaningful relief analysis (66, 67) can be used to compare onset of action of two active drugs.

2. Drug trials dealing with migraine prophylaxis

In general, the subjective nature of migraine and a high placebo effect invalidate open and single-blind trials. However, clinical observation (e.g. 81), may be hypothesis-generating for possible prophylactic effect in migraine.

When a possible prophylactic effect in migraine has been suggested by clinical observations double-blind, randomized, controlled trials should be performed. In these trials the novel drug should be compared with placebo. Its efficacy relative to an established active

comparator should preferably also be evaluated to ensure model sensitivity.

In placebo-controlled trials the drug should be demonstrated to be better than placebo in several studies. In most past trials comparing two active drugs, these have not been found to be statistically significantly different from each other, even if both are superior to placebo. If the results of these trials are reviewed critically (82, 83), it is often apparent that the trials are too small to demonstrate comparability. Furthermore, if both drugs are found effective only by comparison with a baseline period, the improvements noted may be due to the natural history of migraine, amelioration may be due to the passage of time (19). Therefore, comparative trials should also always be placebo-controlled.

The numbers of patients needed (see 2.4) even in crossover trials may require multicentre trials. If enough patients cannot be recruited it is better to avoid doing comparative trials with a low power.

As mentioned in the section on evaluation of results in the planning phase only a few measures should be defined as the primary evaluation measures.

2.1 Selection of patients

2.1.1 Migraine definition

Recommendations: The diagnostic criteria should conform to those of the IHS (*Cephalalgia* 1988; 8(Suppl 7):1-98).

Comments: Diagnostic criteria of the IHS should be adhered to strictly. There are people with attacks that do not meet IHS criteria but, nevertheless, are diagnosed with migraine and respond to migraine therapy. For clinical drug trials, however, requirements are more rigid than in clinical practice. Relatively few people will be excluded by requiring IHS criteria.

The IHS diagnostic criteria classify attacks, and some patients have in their lifetimes attacks both with and without aura. Thus some patients can be classified as having migraine with aura and migraine without aura. If patients are to enter a trial specifically concerning migraine with aura, investigators might arbitrarily require that more than 90% of attacks were with aura during the last 2 years to enhance the probability that the treated attack(s) would be with aura. Similarly, more than 90% of attacks for migraine without aura in over 2 years might be requested in trials concerning migraine without aura (although patients with exclusively migraine without aura are more easily found). Nevertheless, during the trial, each attack should be classified according to the IHS criteria according to clinical features (aura) captured on a diary card.

Regarding the separation of migraine without aura and tension-type headache, investigators should consult the IHS criteria (33).

2.1.2 Other (non-migranous) headaches

Recommendations: Other headaches are permitted if the patient can clearly differentiate them from migraine by the quality of pain (one-sided, pulsating, moderate or severe intensity) and/or by the profile of associated symptoms (i.e. nausea, discomfort to light or sound, visual symptoms or other aura).

Early safety and efficacy studies should exclude other headache.

Comments: Many patients with migraine have so-called *interval headaches* which do not meet IHS criteria for migraine (*Cephalalgia* 1988; 8(Suppl 7):1–96). Future studies may show that interval headaches are indeed fragments of migraine without aura but, for the present, patients who cannot distinguish interval or other non-migrainous headaches from typical migraine without aura must be excluded.

2.1.3 Frequency of attacks

Recommendations: Attacks of migraine should occur 2–6 times per month. The frequency of other headaches should be no more than 6 days per month. There should be at least 48 h of freedom from headache between attacks of migraine.

Comments: The numbers in this section are to some extent arbitrarily derived, but it is important that prophylaxis is clinically indicated in patients who enter prophylactic trials. The recommended frequency of 2–6 attacks per month allows for more rigid standards in certain trials. Other (including interval) headaches of more than 6 days per month would begin to blend into attacks of migraine without aura if migraine were to occur as often as 6 days per month.

Patients may identify relapse or recurrence within 48 h of effective acute treatment as a new attack. Forty-eight hours of freedom between attacks of migraine permits identification of individual attacks and distinction from relapse (recurrence).

2.1.4 Duration of disease

Recommendations: Migraine should have been present for at least 1 year.

Comments: Because there are no objective signs of migraine, a minimum course of 1 year is advisable to help exclude headaches due to organic disease that may mimic migraine, and to establish a stereotyped pattern for the patient's headaches.

2.1.5 Duration of observation

Recommendations: There should be a 3-month well-documented retrospective history and a prospective baseline of at least 1 month.

Comments: The character and especially frequency of headaches as reported retrospectively by the patient are often different when carefully and prospectively observed by the physician and patient. Moreover, patients entering a study often show a change in the frequency of their attacks after enrolment due to inaccurate reporting or regression towards the mean. Prospective observation will best define the baseline frequency and prevent a reported but unreal change in frequency from being attributed to the study drug.

2.1.6 Age at onset

Recommendations: The age at onset of migraine should be less than 50 years.

Comments: Migraine beginning after the age of 50 is rare (<2%) and headache onset in these years is often due to underlying organic disease that sometimes mimics migraine. Few patients will be excluded by this limitation.

2.1.7 Age at entry

Recommendations: Patients may be entered into adult studies between 18 and 65 years of age.

Comments: Drug development programmes may at some point wish to include both younger and older patients. Special protocols will be required for children and adolescents (under the age of 18) (34) in order to show efficacy as well as safety (see 3.4). Migraineurs over the age of 65 rarely need prophylaxis and are subject to cerebrovascular disease and other illnesses that increase the hazard in using experimental drugs.

2.1.8 Gender

Recommendations: Both male and female patients are acceptable.

Comments: There are more women than men in the migraine population. In most migraine trials, however, this female preponderance is exaggerated. Efforts should be made therefore to recruit males to an extent that reflects its epidemiological prevalence (35, 36, 37, 38).

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

Menstrual migraine is discussed in section 3.5.

2.1.9 Concomitant drug use

Recommendations: Appropriate acute therapy must be allowed for individual attacks (see 2.2.10). Other regular concomitant therapy is undesirable.

In early trials of safety and efficacy, the patient should not take any other regular medication. In later trials contraceptive drugs and other drugs not taken for migraine are not contraindicated if there are no important side-effects or potential for clinically significant interaction and the dose has been stable for 3 months. Other migraine prophylactic medication should be discontinued 3 months prior to the drug trial.

Excluded are the following: patients who use drugs excessively for headache (for example, those who regularly take medication for acute headache on more than 10 days per month); patients who have taken antipsychotics, or antidepressant medications (unless only for migraine prophylaxis), during the previous 3 months; patients who abuse alcohol or other drugs (DSM-IV criteria (39)); patients who are allergic or have shown hypersensitivity to compounds similar to the trial drug; patients resistant to all acute migraine drugs prescribed optimally; potentially fertile and sexually active women who do not practise contraception.

Comments: In evaluating a prophylactic drug, other prophylactic drugs and any carry-over effect must be eliminated.

To exclude patients who occasionally use a sedative or minor tranquiliser or to exclude those women who experience no difficulty using contraceptive drugs would too severely limit the population. However, it is necessary to establish any potential for interaction between a test prophylactic drug and contraceptive drugs before women who use them are recruited. On the other hand, it is desirable to eliminate patients who take excessive drugs for the treatment of acute headache or who abuse drugs or alcohol. Those people who are known to be generally resistant to anti-migraine drugs may unfairly bias the study. However, unresponsiveness to medication may be due to inadequate dose, short duration of trial and other factors. These patients are not unequivocally excluded, but criteria for their inclusion should be defined.

2.2 Trial design

2.2.1 Blinding

Recommendations: Controlled trials in migraine prophylaxis should be double-blind.

Comments: The subjective nature of migraine and the high placebo effect (see below) invalidate open or single-blind pilot trials. Drugs for migraine prophylaxis

can therefore only be evaluated with double-blind techniques.

2.2.2 Placebo-control

Recommendations: (a) Drugs used for migraine prophylaxis should be compared with placebo. (b) When two presumably active drugs are compared, placebo control should also be included in order to test the reactivity of the patient sample.

Comments: The placebo effect in migraine prophylaxis is usually in the range 20–40% and in some trials it has been even higher (e.g. 84). A drug must therefore be demonstrated to be superior to placebo. That two presumably active drugs are found equally effective in a trial is no proof of efficacy of either, nor of comparability. To refer to the previous efficacy in other trials of an established drug used as a comparator is not enough; it is using historical controls, a method largely discouraged in medicine. Both drugs should also be shown contemporaneously to be superior to placebo. For further discussion on this point, see the introduction to this section.

2.2.3 Parallel-groups and crossover designs

Recommendations: Either crossover or parallel-groups designs can be used, depending upon the research objectives and drugs under study.

Comments: There was no consensus in the subcommittee on this issue.

The advantage of the crossover design is that it is approximately eight times more powerful than the parallel-groups design in prophylactic migraine trials (85). For certain parallel-groups designs, however, the number of patients required is no more than 2–4 times the number required in a crossover design (86); for further discussion see (24). The drawbacks of the crossover design are: (i) the possibility of a carryover effect; (ii) the need for a long total period of treatment (extended by washout periods) with concomitant increases in dropouts and loss of statistical power; (iii) side-effects which can more easily unmask blinding when a patient is exposed to both treatments; and (iv) at the crossover point, those doing well on active drug are not appropriately treated by switching to placebo, those not effectively treated on active drug are not appropriately treated by switching to placebo, those doing well on placebo no longer need active drug and are not appropriately treated by switching to it. A period effect is not a problem in the crossover design, because suitable statistical techniques can deal with it (19).

2.2.4 Randomization

Recommendations: (a) Patients should be randomized both in crossover and parallel-groups trials in relatively small blocks. (b) For the triple crossover design (two active drugs vs. placebo) the Latin square method should be used. (c) Randomization should occur after the run-in (baseline) period.

Comments: Patients are often recruited to prophylactic migraine trials over extended periods. It is therefore preferable to randomize in relatively small blocks because patient selection may vary with time.

2.2.5 Stratification

Recommendations: In parallel-groups trials, patients should be stratified for frequency of migraine attacks (e.g. <3 or >3 attacks per 4 weeks) occurring during baseline. Stratification is not necessary in crossover trials.

Comments: Randomization alone does not ensure comparability among groups before treatment, and stratification for important prognostic factors should ideally be used. These prognostic factors are, however, virtually unknown in migraine. In some studies (e.g. 87), the extent of the prophylactic effect of drugs has varied depending on baseline frequency. It is therefore reasonable to use frequency of attacks as a basis for stratification, especially because this is the principal outcome measure and baseline equality for this is necessary.

2.2.6 Baseline (run-in) period

Recommendations: A 1-month baseline run-in period is recommended.

Comments: During the baseline run-in period placebo can be given to identify and exclude placebo responders prior to randomization. This will, however, hinder observation of the true placebo response later in the trial; the use of placebo during baseline is therefore optional. If placebo is used, patients must be informed that they will *all* receive placebo for at least a period of 1 month at some time in the trial.

2.2.7 Duration of treatment periods

Recommendations: Treatment periods of at least 3 months should be used.

Comments: Relatively long treatment periods increase the power of the trial by providing more stable estimates of attack frequency. In addition, the efficacy of many drugs accrues gradually (i.e. needs some weeks before becoming fully established). Furthermore, only effects of sufficient duration are clinically relevant. Drugs with

long equilibration half lives may need longer treatment periods of 4–5 months to demonstrate their efficacy.

2.2.8 Washout periods

Recommendations: In crossover trials a washout period of 1 month should be used.

Comments: With prophylactic drugs the benefits of treatment may persist even after treatment is withdrawn. Since drug effects are often slow in onset and wane gradually, a drug-free (placebo) washout period must be interposed between the trial periods. Its length must exceed the time taken to eliminate both the drug and its effect, which is often unknown. A washout period of 1 month is recommended as a practically feasible compromise.

2.2.9 Dosage

Recommendations: In assessing any new drug in migraine prophylaxis no assumptions based on pharmacological activity should be made regarding dosage, since the required mechanism is unknown. Attempts should be made to test as wide a range as possible in different trials. Usually, the no-effect dose and the maximum tolerated dose should both be established.

Comments: As long as the pharmacological basis for the efficacy of prophylactic drugs in migraine remains unknown, the choice of doses in trials is a purely empirical compromise between observed efficacy and tolerability. Whereas dosage of some drugs can be adjusted according to plasma level (e.g. sodium valproate (88) or divalproex (89)) to achieve antiepileptic plasma concentrations, there may be no evidence that efficacy against migraine and plasma levels are related.

The willingness of patients to take the drug for months depends heavily on the ratio between perceived efficacy and side-effects actually experienced. The choice of dose(s) is therefore one of the crucial factors in determining the chances of a successful completion of the trial, whilst this compromise tends to induce the use of suboptimal doses in prophylactic migraine trials.

So far, no dose–response curve has been established for any drug used in migraine prophylaxis.

No less important is the problem of choice of appropriate ('comparable') doses of two or more active drugs in comparative trials. Since information about dose-effect relationships in migraine prophylaxis is lacking, there is no scientific solution but only good clinical judgements as a way forward.

2.2.10 Symptomatic (acute) treatment

Recommendations: Patients should use their usual symptomatic or acute treatment provided that it can be safely

used with the study medication. Such treatment should not be changed during the trial.

Comments: Best possible acute treatment is ethically required in prophylactic treatment trials. In a few previous trials, symptomatic treatment of attacks has been standardized or otherwise regulated, but in such circumstances is unlikely to be optimal for all patients. Many patients have by trial and error found symptomatic treatment giving some degree of relief, and it is unreasonable to ask patients to abstain from such treatment over prolonged periods.

In the cases where patients are using poorly effective drugs or using drugs or drug-combinations suboptimally for symptomatic treatment, the investigator should prescribe the most suitable acute treatment according to standard clinical criteria.

Concerning abuse of analgesics and ergotamine, see 2.1.9.

2.2.11 Control visits

Recommendations: Patients should be seen every 4th week.

Comments: Relatively frequent control visits are important in order to check the headache diary and encourage the patients' continuation in the trial and compliance with medication.

2.2.12 Compliance monitoring

Recommendations: Compliance with prophylactic medication in clinical trials should be promoted by clear explanation of its purpose. In early (proof-of-concept and dose-finding) studies, compliance should be monitored.

Comments: There is evidence that compliance with migraine prophylactic drugs is often poor (90), and their efficacy may be restricted because of this. Early clinical trials in which compliance is not monitored may conclude that a drug has no efficacy when it has not actually been taken. In later trials of effectiveness, a more pragmatic approach to the problem of non-compliance may be acceptable.

2.3 Evaluation of results

2.3.1 Headache diary

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

Comments: The headache diary should be suitable for evaluating the efficacy and tolerability measures chosen from those recommended below. Secondary interpretation by investigators, i.e. investigators' evaluation of

efficacy, is not recommended. The details of diary design are a local issue, subject to language and culture.

2.3.2 Frequency of attacks

Recommendations: Frequency of migraine attacks per 4 weeks should be the primary efficacy measure.

The number of migraine attacks should be recorded irrespective of their duration, and the following rules should be used for distinguishing an attack of long duration from two attacks, or for distinguishing between attacks and recurrences: (a) A migraine attack which is interrupted by sleep, or temporarily remits, and then recurs within 48 h should be recorded as one attack, and not two. (b) An attack treated successfully with medication but with relapse within 48 h counts as one attack. (c) A practical solution to differentiating these using diary entries over the previous month is to count as distinct attacks only those that are separated by an entire day headache-free (see 2.1.3).

Comments: These rules for making distinction between one and two attacks, and relapse/recurrences, are arbitrary but practical (see comments under 2.3.3).

Some trials permit the inclusion of patients with interval headaches, but only if patients are able to differentiate them well from migraine attacks. The headache diary should differentiate between migraine and other headache by simply asking the patient: 'Is this a true migraine attack or another headache?' When identified, other headaches may simply be recorded by the number of days per 4 weeks affected.

Investigators may opt to compare the mean frequencies either during the treatment period and baseline or during the last 4 weeks of treatment and baseline.

2.3.3 Number of days with migraine

Recommendations: Number of days with migraine per 4 weeks can be used as an outcome measure.

Comments: Because of the difficulties mentioned under 2.3.2 with defining the duration of a migraine attack the use of migraine days has been proposed as a simpler alternative (20). This measure, which allows the use of a more simple headache diary, where the patient for each day can indicate whether or not a migraine headache was present, will probably be most useful in large-scale long-term pragmatic trials. In the same diary the patients can also indicate other headaches.

In the earlier phases of drug evaluation, frequency of attacks should be preferred as the primary efficacy measure, since number of days with migraine mixes frequency and duration of attacks whereas the latter variable depends also on acute treatment of attacks. In addition it includes recurrences which may also be determined by acute treatment.

2.3.4 Intensity of headache

Recommendations: The same verbal/numerical scale as given under 1.3.4 should be used: 1=mild headache; 2=moderate headache; 3=severe headache.

Comments: For general comments, see 1.3.4. Furthermore, in prophylactic trials the patient is asked to rate in a single value intensity of headache which at some time is mild and perhaps later severe by 'integrating intensity over time'. It is difficult to give simple or standardized rules for patients to use. Investigators should be aware that patients are probably rating the maximum intensity of headache. Furthermore, acute treatment may modify intensity independently of the trial drug. Intensity of headache should therefore not be used as a primary efficacy measure.

Visual analogue scales are most likely to be too complicated to use in often long-lasting prophylactic RCTs.

2.3.5 Duration in hours

Recommendations: Patients may be asked to record the times each migraine attack starts and ends.

Comments: See comments under 2.3.3. Measurement of duration is difficult because of uncertainties relating to time of onset, time of offset and interaction of sleep. Furthermore, duration of attacks is modified by acute treatment, which cannot be standardized among patients. Duration of attacks should not therefore be chosen as a primary efficacy measure.

2.3.6 'Headache index'

Recommendations: The use of compound headache indices is not recommended.

Comments: Conceivably the headache indices [frequency×intensity] and [frequency×intensity×duration] better reflect the total suffering of patients. There are, however, considerable problems with both intensity and duration (see comments under 2.3.4 and 2.3.5) and, when used in headache indices, faulty weighting in the arbitrary numerical intensity score will be increased by multiplication. Most important, headache indices can in no meaningful way be compared among subjects, and a certain decrease in a headache index is difficult to evaluate clinically. Lastly, there is no need for headache indices because, in most cases where a decrease is found, this is due to a decrease in frequency of attacks (e.g. 91).

2.3.7 Drug consumption for symptomatic or acute treatment

Recommendations: (a) The number of migraine attacks per 4 weeks treated with symptomatic (acute) treatment

may be recorded. (b) The number, e.g. tablets per 4 weeks, should be recorded.

Comments: It is neither ethical nor practically feasible to standardize the symptomatic treatment used by patients during a prophylactic drug trial. There is no satisfactory way of quantifying the consumption of symptomatic medication in relation to the different drugs used by the patients. For the moment, the simple qualitative record of whether or not a symptomatic treatment was taken during an attack can be supplemented by a count of dosage units. This can only be a secondary outcome measure.

In within-patient (crossover) comparisons, acute drug consumption may have value. Its use even as a secondary measure is dubious in between-patient comparisons.

2.3.8 Patients' preferences

Recommendations: The use of patients' preferences is not recommended.

Comments: Patients' preferences for one or other treatment can be asked only in a crossover trial. It is not recommended because it can endanger the blinding of patients since the design of the study has to be disclosed.

2.3.9 Responder rate (50% improvement)

Recommendations: Responder rate is defined as the percentage of subjects in a treatment group with 50% or greater reduction in attack frequency during treatment compared with the baseline period.

Comments: The choice of 50% or greater reduction is traditional and arbitrary, and the investigator (or patient) should be the judge of what is considered a good response. This dichotomous measure is relatively insensitive to treatment effects, but may be used to identify a subgroup of responders in *post hoc* analysis; any finding will need to be confirmed in prospective trials with the main objective having this group in mind. Use of this measure can therefore, in most trials, be considered only as an hypothesis-generating exercise. Results of this sort (responder rate) are particularly vulnerable to selection bias, limiting the generalizability of the study results.

Responder rates can be used in meta-analyses of placebo-controlled RCTs.

Alternatively, time series analysis (21, 92) can be used in defining responders.

2.3.10 Adverse events

Recommendations: Adverse events during treatment should be recorded. Spontaneous reports supplemented

by response to open questions are recommended. Adverse events should be rated as mild, moderate or severe; serious or non-serious; the time of occurrence and duration should be noted; also to be recorded is whether an adverse event led to discontinuation of treatment. Serious adverse events must be handled according to GCP guidelines (74, 75).

Comments: Adverse events tend to occur before efficacy, and in clinical practice they are a major problem in prophylactic migraine treatment, often leading to discontinuation of treatment. Incidence of adverse events, especially adverse events leading to discontinuation of treatment, should therefore be regarded as one of the major measures for judging a prophylactic migraine drug.

Nevertheless, adverse events, unwanted effects that occur during treatment (18), 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 adverse event was drug-related. It should be noted that regulatory authorities require more detailed reporting of adverse events with new drugs (74, 75).

2.4 Statistics

In the parallel-groups design comparisons between groups can be made either as direct comparisons during the treatment periods or as comparisons of changes from baseline. The latter is conceivably more powerful, but analyses have so far shown only that this is marginally so [Tfelt-Hansen, personal observation]. In parallel-groups trials the use of the baseline value as a covariate can also be examined but results of this analysis should be judged with caution (93).

Suitable statistical methods (19) can be used in the crossover design for correction for a period effect ('time effect'), if present.

Confidence intervals for differences are recommended (18) in order to inform the reader fully of the meaning of results of the trial. A statement that two drugs are comparable without giving confidence intervals is unacceptable.

3. Special comments

3.1 Role of health-related quality of life (HRQOL) measures

End-points currently used in migraine trials are statistically powerful but almost certainly do not well reflect patients' values. There are ongoing efforts to invent more clinically relevant measures.

To evaluate the total impact of headache and headache therapies on the individual sufferer, outcomes research is emerging as an important tool. The full range of outcome measures in headache includes clinical evaluations, economic assessments and humanistic measures. Of increasing importance is the impact of clinical measures on patient-perceived quality of life, work performance and economic cost. Health-related quality of life (HRQOL) represents the net effect of an illness and its consequent therapy on a patient's perception of his or her ability to live a useful and fulfilling life (94, 95).

HRQOL can be measured with a variety of generic and specific questionnaires. Generic questionnaires are usually chosen for comparisons between study populations and different diseases, whereas disease-specific questionnaires are designed to assess problems associated with a single disease or treatment. To be scientifically robust measures of outcome, all such instruments need to be reliable, validated and sensitive to clinically relevant changes.

Instruments for measuring HRQOL in migraine 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 and combinations of HRQOL instruments and clinical outcomes have been reported, and their use is becoming widely accepted, whilst no single instrument has yet been recognized as the gold standard in migraine HRQOL assessment. The future of HRQOL research may see the evolution of combined generic and specific instruments.

Results to date have focused on group means; the interpretation of HRQOL changes for individual patients is not yet available. Therefore, applications for clinical practice apart from the clinical trial setting have not been fully appreciated. In addition to pharmaceutical interventions, other specific components of headache therapy must eventually be analysed to determine their impact on HRQOL, which may represent the final common pathway of all the physiological, psychological and social inputs into the therapeutic process. In future clinical trials, controls for the impact of changes over time in all of these, for whatever reason, may be necessary.

Generally, HRQOL measures are better suited for long-term prophylactic RCTs than for studies where effects of short-term (acute) treatment are measured. They are the likely basis for trials comparing acute therapy alone with acute plus prophylactic therapy, which address a highly important clinical question but for which no designs are yet available.

Disability-adjusted life years (DALYs)

One measure of the impact of disease, potentially applicable before and after treatment, is disability-adjusted life years (DALYs) (96, 97). This concept, promoted by the World Health Organization for all disabling illness, is a measure incorporating both mortality and disability. Thus, a disease that ends the life of a man 20 years before expectation imposes 20 DALYs. A non-fatal illness that causes 50% disability 40 years before death, without shortening life, also imposes 20 DALYs. Methods exist or are being developed, using appropriate weighting, for estimating disability associated with specific illness.

Where the disabling effect of illness is continuous, calculation of DALYs depends in a relatively simple way on duration, or age at onset if it is permanent. In episodic illness (migraine, for example), calculations are based on estimates of attack-related disability, duration of illness from onset and incidence of attacks: DALYs accrue with each attack over the lifetime of the illness. But, in addition, although symptoms are in total remission between attacks, it is recognized that many migraine sufferers are nonetheless affected interictally by conditions such as migraine, making modifications to their lifestyles in expectation of or endeavouring to prevent the next attack. These compromises should be included in the disability estimate and, being continuous, may add up to the larger share of the total impact.

Methodology does not yet exist to apply DALYs to headache disorders such as migraine. However, a collaboration between WHO and IHS is expected to develop proposals, which should in due course be adapted for and tested in treatment trials.

3.2 Sources of patients

Migraine sufferers attending specialist clinics may not be representative of the larger number seen by primary care physicians, although there is little formal evidence of significant differences between these. Neither group is likely to match those in the general population who do not seek medical advice.

Clinical trials need to recruit widely from the population who will use the drug when marketed. Early (phase II) migraine trials may be more readily conducted in specialist centres where resources exist to carry them out. In later development, patients should be enrolled from primary care with as few restrictions as possible. It is not known whether advertising to the general public for clinical trial subjects produces a representative sample of migraineurs.

3.3 Patients who have already participated in several trials

It is ethically undesirable to include the same patients in trial after trial. From the scientific point of view, patients who make themselves available for multiple trials may not fairly represent the target population.

*3.4 Trials in children and adolescents**Drug trials dealing with acute treatment*

Few randomized clinical trials of drugs for acute migraine have been performed in children or adolescents (e.g. 98–105), and even fewer have shown efficacy. The reasons for lack of effect in children and adolescents of drugs such as oral sumatriptan, which are clearly effective in adults, are uncertain. Difficulty in demonstrating efficacy has been attributed to the high placebo response (up to 50%) seen especially in children (99), itself perhaps explained by the natural course of attacks which tend to be shorter in children and adolescents than in adults. In addition, the tendency of children to try to sleep in order to end a migraine attack makes assessment over time after treatment problematic.

In the selection of children and adolescents for clinical trials, those with untreated attack durations longer than a few hours are more likely to demonstrate beneficial treatment effects (104). It may be appropriate to select these, since they are in greater need of drug treatment, rather than allowing the attack to run its course. However, results cannot then be generalized to all children and adolescents.

It has been suggested that sleep should be a success criterion for children (104). Adolescents on the other hand generally do not wish to sleep (104). Otherwise, in the absence of good experience the recommended primary efficacy end-point is pain-free at 2 h (see 1.3.2) in selected or unselected children and adolescents, as in adults. Time to onset of relief is probably a good secondary measure in adolescents (for discussion, see (104)).

Drug trials dealing with prophylactic treatment

In a meta-analysis of behavioural and prophylactic pharmacological intervention studies in paediatric migraine (106) it was observed that very few high-quality randomized clinical trials of drug prophylaxis existed, and their results were generally contradictory.

There is no special guidance available on selection of children or adolescents for trials of migraine prophylactic drugs. In such trials, particular emphasis should be placed on recording and evaluating adverse events such as sedation, which is a particular problem for these age

groups. Selection of doses used in prophylactic trials is therefore crucial.

It is most likely wise to use a simple headache diary, and days with migraine as the primary efficacy measure. The limited experience available (107, 108) indicates that children co-operate well in prophylactic drug trials and there is no need for shorter treatment periods than the 3 months recommended for adults (see 2.2.7).

3.5 Trials in menstrual migraine

In menstruating females the peak incidence of migraine during the cycle is in the interval beginning 2 days before and extending through the first few days of menstruation (109). MacGregor (27) suggested that 'menstrual migraine' should be defined as migraine attacks occurring within day 1 ± 2 days of menstruation (i.e. on or between 2 days prior to menstruation and the first 2 days of menstruation) and at no other time of the cycle. In the IHS headache classification (33) it is stated: 'Migraine without aura may occur almost exclusively at a particular time of the cycle-so-called "menstrual" migraine. It seems reasonable to demand [for such a diagnosis] that 90% of attacks should occur between two days before menses and the last day of menses, but further epidemiological knowledge is needed'. In one study (110) only 7% of female patients had pure menstrual migraine.

Drug trials dealing with acute treatment

Migraine attacks occurring in association with menstruation are generally noted to be severe, of long duration and difficult to treat. A drug trial concerning acute treatment might therefore investigate whether a drug is effective in menstrually associated migraine attacks (in patients with other attacks during the cycle) or pure menstrual migraine or both. A specific aim of such a trial might be to show the effect of a new drug on relapse rate (recurrences) compared with standard drugs.

If the effect of a drug on pure menstrual migraine is to be investigated it is recommended that patients record their migraine attacks and menstrual periods prospectively in a headache diary for 2–3 cycles before they enter the trial. This will distinguish them from patients with the more common menstrually associated migraine. If the aim is to investigate the effect of a drug on menstrually associated migraine attacks this is unnecessary but patients should, after randomization, keep a headache diary also reporting menstruation, treating only one or more menstrually associated attacks with the test medication.

In either case, patients need careful instruction on allowable limits for the temporal relationship between the migraine attack and the first day of menstruation. In

the case of pure menstrual migraine a strict definition, as above, should be applied.

The primary efficacy measure should be the percentage of patients pain-free at 2 h (1.3.2) but, in these often long-lasting migraine attacks with a high risk of relapse, sustained pain-free (1, 3, 3) will be an interesting measure.

Drug trials dealing with prophylactic treatment

Standard methods may be employed. However, in the prophylaxis of menstrual migraine, with predictable attack onset, there is the option to use treatment only perimenstrually and not throughout the whole cycle. Depending on the putative mechanism of action, perimenstrual treatment can be started from 1 week (e.g. 111) to 48 h (e.g. 112) before the predicted onset of a migraine attack and continued into the menstruation period if necessary. It is recommended that patients, before entering a trial of such treatment, prospectively document a stable temporal relationship between attacks and menstruation for 2–3 months in a headache diary.

Both crossover and parallel-groups designs can be used. Using the crossover design the efficacy of perimenstrual oestrogen supplementation by percutaneous gel has been demonstrated in two relatively small trials ($n=18$) in pure menstrual migraine (112) and in menstrually associated migraine (113), illustrating the power of this design (for a review of these and other trials, see (27)). The possibility of a carryover effect, one drawback of the crossover design (see 2.2.3), is unlikely when drugs are administered only perimenstrually.

The primary efficacy measure should be the number of migraine attacks per patient-cycle in each treatment group. Secondary measures could be severity of attacks as rated by the patients and drug consumption for symptomatic treatment per attack.

3.6 Publication of results

'Publication of research is an ethical imperative (114). Medical knowledge worldwide is developed in part on the published results of previous research work. Future research properly takes into account all that has been done before. Both are at risk of being misled if publications present only a partial account of past research, especially if the part that is missing is "selected" (28).'

Headache treatment, as any other, should be based as far as is possible on evidence of efficacy, tolerability, and safety in the proposed use. The most reliable evidence for efficacy and tolerability is from randomized clinical trials (RCTs), and the best evidence is gained by a critical overview of all such RCTs that have been done. This requires all such RCTs to be in the public domain.

This Subcommittee therefore strongly supports one of the firm recommendations of the Ethics Subcommittee of IHS (28): '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 nonpeer reviewed supplements is unacceptable.'

The publication should conform to generally accepted rules for reporting RCTs (115).

Investigators and sponsors should negotiate time-lines for publication at the onset and ideally they should form part of the protocol.

4. Checklists (numbers refer to those in the main text)

4.1 Acute attack treatment

1.1 Selection of patients

1.1.1 Migraine definition

Use diagnostic criteria of HIS

1.1.2 Interval headaches

Permitted if well-recognized by the patient

1.1.3 Frequency of attacks

Migraine attacks 1–6/month, other (including interval) headaches <6 days per month.

1.1.4 Duration of disease

>1 years

1.1.5 Duration of observation

3 months retrospective or 1 month prospective recording.

1.1.6 Age at onset

<50 years

1.1.7 Age at entry

18–65 years

1.1.8 Gender

Both female and male patients

1.1.9 Concomitant drug use

See text

1.2 Trial design

1.2.1 Blinding

Use double-blind technique

1.2.2 Placebo control

Recommended, see text

1.2.3 Parallel-groups/crossover

Use both designs, see text

1.2.4 Randomization

Essential

1.2.5 Stratification

Not recommended in outpatients trial, see text

1.2.6 Dose–response curve

Should be defined, see text

1.2.7 Route of administration

In early trials use parenteral route, if possible

1.2.8 Time of administration

See text

1.2.9 Number of attacks treated with the same treatment

One attack, see text

1.2.10 Rescue medication

Allowed after <2 h

1.2.11 Consistency of response

See text

1.3 Evaluation of results

1.3.1 Attack report form

Use a simple report form

1.3.2 Percentage of patients pain-free within 2 h

Should be primary measure of efficacy, see text

1.3.3 Sustained pain-free (pain-free within 2 h, no rescue medication, and no relapse/recurrence)

Should be a secondary efficacy measure, see text

1.3.4 Intensity of headache

Use a 4-point verbal/numerical scale or a visual analogue scale

1.3.5 Percentage of patients with a decrease of headache from severe or moderate to mild or none within 2 h (headache relief)

Should be a secondary efficacy measure, see text

1.3.6 Time to meaningful relief

Can be a secondary efficacy measure, see text

1.3.7 Duration of attacks

Should not be used, see text

1.3.8 Speed of onset of action

See text

1.3.9 Rescue medication

Can be used as an efficacy measure

1.3.10 Global evaluation of medication

Use a 5-point verbal scale

1.3.11 Functional disability

Use a 4-point verbal/numerical scale

1.3.12 Presence of nausea and/or vomiting

Should be recorded

1.3.13 Presence of photophobia and phonophobia

Should be recorded

1.3.14 Adverse events

Should be recorded, see text

1.3.15 Patients' preference

Should be used in crossover trials, see text

1.3.16 Incidence of relapse (recurrence)

Should be recorded, see text

1.3.17 Treatment of relapse	Pain-free within 2 h, see text
1.3.18 Consistency of response	See text
1.4 Statistics	
Sample size calculations	Use primary efficacy measure, see text
Confidence intervals	Are recommended
4.2 Prophylactic treatment	
2.1 Selection of patient	
2.1.1 Migraine definition	Use diagnostic criteria of HIS
2.1.2 Other (including interval) headaches	Permitted if well-recognized by the patient
2.1.3 Frequency of attacks	Migraine attacks 2–6/month, other headaches < 6 days per month > 1 years 3 months retrospective and 1 month prospective recording
2.1.4 Duration of disease	< 50 years
2.1.5 Duration of observation	18–65 years
2.1.6 Age at onset	Both female and male patients
2.1.7 Age at entry	See text
2.1.8 Gender	
2.1.9 Concomitant drug use	
2.2 Trial design	
2.2.1 Blinding	Use double-blind technique
2.2.2 Placebo control	Recommended, see text
2.2.3 Parallel-groups/crossover	Use both designs, see text
2.2.4 Randomization	Randomize in small blocks
2.2.5 Stratification	Stratify for number of attacks during baseline
2.2.6 Baseline recording	A one-month baseline should be used, see text
2.2.7 Duration of treatment periods	At least 3 months
2.2.8 Washout periods	One month in crossover trials
2.2.9 Dosage	Use as wide a range of doses as possible
2.2.10 Symptomatic treatment	Keep usual treatment constant during the trial
2.2.12 Control visits	Every 4th week
2.3 Evaluation of results	
2.3.1 Headache diary	Use is recommended
2.3.2 Frequency of attacks	Number of attacks per 4 weeks should be the primary efficacy measure, see text
2.3.3 Duration in hours	Should be recorded, see text
2.3.4 Intensity of headache	Use a 4-point verbal/numerical scale
2.3.5 Duration in hours	Should be recorded, see text
2.3.6 Headache index	Not recommended, see text
2.3.7 Drug consumption for symptomatic treatment	Should be recorded, see text
2.3.8 Patients' preferences	Not recommended
2.3.9 Responders(50% effect)	Can be hypothesis generating, see text
2.3.10 Adverse events	Should be recorded, see text
2.4 Statistics	
Sample size calculations	Use frequency of attacks, see text
Model	Separate therapeutic and 'time effect' in crossover trials, see text
Confidence intervals	Are recommended

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