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Guidelines for controlled trials of drugs in migraine: Third edition. A guide for investigators

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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' overarching goal was to improve 'the quality of controlled clinical trials in migraine', which could be achieved by using scientifically robust methods of clinical research. The report highlighted the complex nature of migraine clinical trial methodologies and offered a road map to clinical investigators who were interested in the field. The Migraine Guidelines were adopted widely (2–7), although – for a variety of reasons, including regulatory restrictions – not universally (8–11), and this was the impetus for the development of similar guidelines

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for tension-type headache (12,13) and for cluster headache (14).

The second edition of the guidelines was published in 2000 (15) and, based on the second edition, the European Medicines Agency published in 2007 'Guidelines on Clinical Investigation of Medicinal Products for the Treatment of Migraine' (16).

Have investigators then followed the recommendations in these guidelines for randomized controlled trials (RCTs)? Unlike the case of RCTs for migraine prevention where the recommended primary efficacy measure of migraine attack frequency was used in 72% of 52 RCTs (17), adherence to the recommendations in the guidelines for acute migraine treatment has not been overwhelming. Indeed, the recommended measure of freedom from pain after 2 h was the primary efficacy measure in 31% of 145 acute RCTs between 2002 and 2008 (17). Instead, headache relief after 2 h (a decrease from moderate or severe to none or mild) was used in 39% of such trials. Notwithstanding, the proportion of RCTs using pain freedom as the primary efficacy measure has continued to increase over time (17), and is even used in recent large clinical trials (18–21).

Following the publication of the IHS Clinical Trials Guidelines, several clinical drug development programmes emerged, notably for acute migraine (e.g. 5-$HT_{1B/D}$ agonists, triptans) and for prevention (e.g. topiramate). The majority of these RCTs were performed mainly for registration purposes (16). This exponential increase in migraine clinical research, the accumulating experience of clinical researchers and the pharmaceutical industry alike, and the trend towards large multi-centre and multi-national studies, call for a timely revisit and a refresh of the original guidelines and their second edition.

The third edition of Migraine Clinical Trials Guidelines is a consensus summary that was developed by experts in the field, and its purpose is to recommend a contemporary, standardized, and evidence-based approach to the conduct and reporting of migraine RCTs.

Broader discussions of clinical trials methodologies can be found elsewhere (22–30). Also, ethical considerations in migraine clinical research have been published separately (31). Finally, it should be noted that the revised Guidelines represent Research Practice Parameters and are the highest level in the hierarchy of Evidence-Based Recommendations in the absence of published Standards of Research Practice. Therefore, the IHS endorses the adherence to the Guidelines unless there is scientific justification for deviations from the recommendations.

The Third Edition of The Migraine Clinical Trials Guidelines is organized similarly to the previous two editions. Notably, RCTs for acute attacks of migraine are addressed in the first section of these guidelines and are followed by discussions and recommendations relating to RCTs for migraine prevention, including short-term prophylaxis or 'mini-prophylaxis' for predictable migraine attacks, such as those associated with menses (32). Sub-sections include: patient selection, trial design, evaluation of results and statistics. A toolbox for each type of trial (acute and prevention) is provided at the end.

1 Drug trials for the treatment of acute migraine attacks

Investigators should be aware of several challenges that could be encountered in trials dealing with the treatment of the acute migraine attack. Notably, the following factors should be considered when designing the trial:

a. The headache of migraine is not a stable pain but develops gradually, or sometimes rapidly, to a peak with subsequent spontaneous resolution. This poses challenges regarding the timing of intake of test medication, which might be early or when the attack is fully developed, and in the evaluation of results.
b. 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 (33,34).
c. There is high between-participants and smaller within-participants variability (35,36).

1.1 Patient selection

1.1.1 Migraine definition. Recommendations: Eligible patients should fulfil ICHD-II diagnostic criteria for migraine (37).

Comments: ICHD-II migraine diagnostic criteria of the IHS (37) should be adhered to strictly, particularly in early phases of a new drug development in order to avoid diagnostic uncertainties, which lead to population heterogeneity and possible type-2 error. The IHS diagnostic criteria classify attacks, and some patients have in their life time attacks both with and without aura. Given that the aura is normally easy to diagnose, patients with both migraine without aura and migraine with aura can normally be included in trials focusing on migraine with aura. They are needed because most patients with frequent attacks with aura also have attacks without aura and these are precisely the patients one would like to enter in a drug trial. During the trial

in patients in both types of attacks, each attack should be classified according to IHS based on clinical features that are captured in a diary. In early migraine without aura trials only patients with this type of migraine should be included. In later trials (late phase III and phase IV), patients with both types of migraine can be included in order to make the study more naturalistic.

Theoretically, during the trial each attack should be classified according to the IHS criteria and based on clinical features that are captured on a diary. However, the clinical features of a migraine attack can be modified by treatment, which would render such a strict requirement impractical. Regarding the separation of migraine without aura and tension-type headache, consult the IHS criteria (37). For trials in migraine with aura, see section 3.1.

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 (nausea, discomfort to light or sound, visual symptoms or other aura), or both. Early safety and efficacy studies should exclude participants with headaches that overlap with the headache type under study over the predefined study period.

Comments: Many patients with migraine have non-target headaches that do not meet IHS criteria for migraine (37). Future studies may show that non-target headaches are indeed fragments of migraine without aura but, for the present, patients who cannot distinguish non-target or other, non-migrainous headaches from typical migraine without aura should not be included.

1.1.3 Frequency of attacks. Recommendations: Attacks of migraine should occur 1–6 times per month. The frequency of other (including non-target) headaches should be no more than 6 days with headache per month. There should be at least 48 h of freedom from headache between attacks of migraine.

Comments: In order to avoid very lengthy 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. This ensures that patients with medication overuse headache (MOH) and those with chronic migraine are excluded. 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.

1.1.3a Medication overuse headache and chronic migraine. Recommendation: Patients with medication overuse headache and chronic migraine patients ($\geq$ 15 headache days/month) should be excluded. For RCTs in chronic migraine, see (38).

1.1.4 Duration of disease. Recommendations: Migraine should have been present for at least 1 year prior to eligibility for the study.

Comments: The 1 year requirement increases the specificity of the diagnostic criteria because more accurate or valid surrogate measures are lacking. Because there are no objective signs of migraine, a minimum course of 1 year is advisable to help exclude other types of headaches that 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 IHCD-II criteria (37).

1.1.5 Duration of observation. Recommendations: There should be a 3 month well documented retrospective history.

Comments: Prospective observation period of 1 month is advisable, although such a requirement may be impractical.

1.1.6 Age at onset. Recommendations: The age at onset of migraine should be less than 50 years in exploratory trials such as phase II trials and early phase III trials.

Comments: Migraine beginning after the age of 50 years is rare (<2%) and the prevalence of organic disease mimicking migraine increases after age 50 years. Consequently, few patients will be excluded when applying this entry criterion. However, the inclusion of participants with onset of migraine after 50 years of age is advisable in confirmatory and pragmatic clinical trials (phase IIIb and phase IV) as long as the diagnosis of migraine is well established by ICHD-II criteria (37).

For trials in children and adolescents, see section 3.5.

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

Comments: The inclusion of patients over 65 years old is encouraged in pragmatic trials.

The efficacy and safety of experimental drugs or devices in older (> 65 years) and younger (< 18 years (39), see section 3.5) patients are often short-lasting in children and placebo response is high (see special

comments). Migraineurs over 65 years old are more likely to have co-morbidities than the younger population, which could require particular attention to safety and drug-drug interactions.

1.1.8 Gender. Recommendations: Male and female migraineurs are eligible participants for migraine RCTs.

Comments: Migraine is at least 3 times more prevalent in women than in men, and this ratio is amplified in RCTs. Efforts should be made to recruit males to an extent that reflects the prevalence of migraine in men (40–43). As with any clinical drug development of a new chemical entity, cautions should be taken to avoid enrolling women who may be pregnant or lactating, unless such populations are the target of the study. Menstrual migraine is discussed in section 3.6.

1.1.9 Concomitant drug use. Recommendations: All concomitant therapy that is allowed (openly or on a restricted basis) should be specified. In phase II and early phase III clinical trials of safety and efficacy, participants should not be allowed concomitant therapies, unless there is clear evidence of a lack of drug-drug interactions (pharmacokinetic and pharmacodynamic). In later drug development trials (i.e. Phase IIIb and Phase IV), contraceptive drug use, drugs given for migraine prophylaxis and drugs not taken for migraine may be specifically permitted with due precautions.

If considered exclusionary, the withdrawal of migraine prophylactic drugs prior to study entry, should be completed at least 1 month prior to enrolment. In the rare occasion when a prophylactic drug has a very prolonged half-life, ensuring that at least 10 half-lives have elapsed before enrolment is recommended. When migraine prophylactic drugs are permitted in the study protocol, enrolled participants should have been on a stable dose of no more than one prophylactic agent for at least 3 months in order to ensure a stable baseline and avoid the introduction of potential confounding variables.

Participants who use drugs excessively for headache (for example, regular intake of triptans for acute headache on more than 10 days per month; meeting ICHD-II criteria for probable medication overuse headache) should be excluded.

It is recommended to exclude from Phase II and IIIa RCTs those participants who have used neuropsychiatric medications (e.g. antipsychotics, antidepressants) for conditions other than migraine prophylaxis during the 3 months prior to consideration for enrolment.

Comments: Evaluating the potential for drug interaction(s) is an important aspect of drug development prior to marketing. The absence of a clear understanding of pharmacokinetic and pharmacodynamic drug-drug interactions can obscure the interpretation of treatment effects or side effects. The exclusion of participants who occasionally use a sedative or a minor tranquilizer is not practical in Phase IIIb, Phase IV or pragmatic trials. Also, the exclusion of women who experience no difficulty using contraceptive drugs is impractical and limiting in such trials, unless there are clearly identified or expected drug-drug interactions.

The recommendation to exclude participants who take excessive drugs for the treatment of acute headache is based on evidence that the pathophysiology and response to treatment are likely to be altered in such populations. This evidence applies to people who abuse substances in general, including those who abuse alcohol.

People who are known to be generally resistant to anti-migraine drugs may unfairly bias a RCT for acute migraine if they are overrepresented inadvertently in the study population. Notwithstanding, a history of poor response to medication may result, among other factors, from inadequate dosing, short duration of trial, or frequent recurrence – despite initial relief – that is perceived as drug failure or resistance. Therefore, the investigator should establish the true nature of 'drug resistance' before excluding any participant from entering into the study.

1.2 Trial design

1.2.1 Blinding. Recommendations: All efficacy trials of acute migraine treatment should be double blind.

Comments: Drugs used for acute treatment of migraine can be reliably evaluated only in randomized, double-blind clinical trials. Long-term safety trials and naturalistic trials do not need to be blinded. Triple blinding, that is, participant-blind, investigator-blind and sponsor-blind (statistician or other personnel evaluating the study results) may be beneficial when data evaluation can introduce an undue bias on study results.

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 participant population.

Comments: Placebo response rate for headache relief in the treatment of migraine attacks varies from 6% (44) to 47% (45), and the mean was 29% in a meta-analysis of 98 studies (46).

In contrast, the placebo response for pain freedom is reported to be 5–7% (47), with a mean of 9% in the aforementioned meta-analysis (46). These wide ranges of placebo response make it difficult to interpret the

results of an active-control trial that does not include placebo and that draws upon external information (the argument of 'assay sensitivity').

1.2.3 Parallel-group and crossover designs. Recommendations: Both parallel-group and crossover designs can be used.

Comments: The parallel-group design has the advantage of simplicity. Parallel-group studies have successfully demonstrated both superiority and comparability among drugs (7,48,49). With a crossover design, a period effect may occur although there is probably no risk of carry-over effect in acute treatment trials of drugs for migraine. The crossover design allows robust estimates of intra-individual consistency of response using placebo-control groups (50). In addition, the crossover design allows for preference assessments of benefit/tolerability ratios of an active vs. placebo, two actives, or two different doses, on the assumption that proper statistics are applied to evaluate preference (51). Crossover designs are well suited for surrogate studies and pragmatic trials where intra-individual comparisons are desired.

1.2.3a Sequential, step-wise design. Recommendations: In phase II group-sequential, adaptive treatment, dose-defining, randomized controlled trials can be used.

Comments: 'Non-traditional' clinical trial designs are becoming more commonplace in migraine clinical trials. These include: step-wise, adaptive, enriched designs and futility trials. Adaptive designs allow the modification of aspects of a trial while in progress without undermining its scientific validity or integrity. Randomized group-sequential, adaptive treatment, dose-defining proof-of-concept designs can be used in phase II for evaluation of the optimal dose of a drug (52,53). Alternatively, a two-step, adaptive, dose-ranging design can be used (18). The major advantage of these designs is that they allow evaluation of the optimal dose over a wide dose range in relatively few patients (52,53). The chosen dose(s) can then be confirmed as the optimal dose(s) in phase III.

1.2.4 Randomization. Recommendations: Study participants should be randomized to one of the study arms in both crossover and parallel-groups trials. Randomization should occur at entry to the trial, except when considering adaptive randomization.

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

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

Comments: Randomization alone may not ensure full comparability between participants in different treatment groups, and stratified randomization is sometimes used to circumvent potential imbalances between treatment groups. According to the European Agency for Evaluation of Medicinal Products, 'stratification variables, regardless of their prognostic values, should usually be included as covariates in the [study] primary analysis.' Furthermore, stratification by important prognostic factors should be limited to only a few and only to those that historically have a clearly demonstrated impact on the primary study outcome. Certain stratification variables that have been used in acute migraine trials have included age, body weight, type of migraine (with or without aura) and headache intensity at baseline. Migraines with and without aura appear to respond similarly to medication (9). Age and body weight have been shown to predict treatment response in some studies (54). Similarly, the intensity of headache pain at the time of treatment had an effect on the primary outcome in a number of triptan migraine RCTs, particularly in inpatient studies (55).

1.2.6. Intention to treat. Recommendations: Randomized controlled trials in acute migraine should follow the principle of intention to treat, which implies that study data are analysed based on the original allocation of study participants, regardless of treatment received. Withdrawals, participants lost to follow-up and participants who did not adhere fully to study protocols should not be excluded from the primary analyses.

Comments: Explicit statements about post-randomization exclusions should replace the ambiguous terminology of modified intention to treat (56).

1.2.7 Dose-response curves and dosage. Recommendations:

a. Dose-response curves should be defined clearly in early (phase I–IIb) randomized clinical trials of new chemical entities for the treatment of acute migraine.
b. Efficacy- and tolerability-based minimum effective and optimal doses should be determined.
c. Effective doses of a well established or standard drug should be used in comparative randomized clinical trials, unless clinically inappropriate, in which case a clear justification for the particular dose selection should be given.

Comments: Dose-response curves, optimal efficacy- and tolerability-based doses have been established for many triptans (2–7,57,58). Accordingly, the

comparison of a new chemical entity with a standard drug such as a triptan should include in the comparator arm(s) migraine-effective dose ranges of the standard drug. Occasionally, the demonstrated efficacy of the comparator drug is established in other disease states such as pain, or the dose-response curve of the comparator is not well characterized. In these instances, the accepted optimal therapeutic dose of the comparator should be tested against the new chemical entity.

1.2.8 Route of administration. Recommendations:

a. Parenteral therapy is a preferred route of administration of a test drug in early efficacy trials where the drug mechanism is novel (Phase Ib and IIa; proof of concept or principle).
b. When pre-clinical and early pharmacokinetic (PK) data demonstrate an acceptable PK profile (e.g. good oral bioavailability, rapid oral absorption), oral administration of the test drug is recommended in later clinical trials (Phase IIb, III) because the oral route is preferred by most migraineurs.
c. Alternative routes of administration (e.g. transdermal, inhalational, buccal, intranasal, rectal) to the oral method can be used, especially in severely nauseated patients.

Comments: Intravenous administration optimizes drug delivery, mitigates PK factors related variances and minimizes the potential effects of PK profiles on pharmacodynamic parameters (e.g. pain). Consequently, the efficacy and tolerability of an intravenously administered drug are better understood. Investigators should be aware that oral absorption of drugs can be delayed during migraine attacks (59–62). Therefore, it is advisable to establish the PK profile of an oral test drug during and outside a migraine attack, using a crossover design in early phase Ib trials, in order to gauge dose selection in later efficacy trials.

1.2.9 Timing of administration. Recommendations: Either early in the attack or after an attack is fully developed is acceptable as the timing for test drug intervention (for migraine with aura, see section 3.1).

Comments: In principle, study drug administration should be started as early as possible during the headache phase in order to mimic clinical practice. However, patients with migraine without aura may have difficulties in distinguishing between a migraine and interval or other headache type at the beginning of an attack and may mistakenly treat other headaches. This potential confusion is mitigated when a headache is fully developed. 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. Accordingly, and depending on the specific objectives of the study, both early intervention strategies and treatment when the headache is fully developed – for example, for early morning migraine (63) – should be considered when investigating the efficacy, safety and tolerability of a test drug in acute migraine.

1.2.10 Number of attacks treated with same treatment. Recommendations: The effect of a drug on one attack of migraine should be the primary objective in both crossover and parallel group trials.

Comments: Efficacy trials (for trials addressing consistency as a primary objective, see section 1.2.12 (8,57)) that test the effect of a drug on several migraine attacks may increase the study's discriminative power when outcome measures are averaged across multiple attacks and for each participant. This approach was recommended previously (1). However, the desired increase in study power can be counterbalanced by a decrease in number of participants fully completing the trial. Indeed, trials that require multiple attack treatments (i.e. more than three) to assess efficacy and safety probably increase the dropout rates, which could introduce an unmanageable bias if dropout is related to tolerability issues or ineffectiveness (64,65). Furthermore, repeated intake of placebo when a standard treatment is available can pose some ethical issues.

1.2.11 Rescue medication. Recommendations: A rescue medication should be allowed any time after the first primary efficacy time point. Typically, this is 2 h after initial test drug administration.

Comments: The time interval to using rescue medication can be reduced when the first primary efficacy time point is less than 2 h, which is often the case in trials of parenteral investigative drugs. Little can be learned from delaying rescue medications beyond the primary efficacy time point. Furthermore, such a delay may cause undue discomfort to the study participant, which is ethically unacceptable.

1.2.12 RCTs evaluating consistency of response (pain freedom at 2 h). Recommendations: Consistency of response should be evaluated in multi-attack, double-blind, placebo-controlled and crossover RCTs. The optimal number of attacks treated is five; active treatment is used for four attacks and placebo for one.

Comments: Admittedly, the choice of five attacks in a consistency RCT is empirical. Consistency of headache response cannot be established in studies that are intended primarily for assessing long-term safety because: (1) often, a placebo control is not included; and (2) long-term safety studies often introduce selection bias when responders to treatment in the

double-blind efficacy trials are rolled over into the long-term study (e.g. (66)).

Two study design approaches can be considered for consistency trials. One approach is to treat all participants with active drug for four of five attacks and with placebo for one; the choice of placebo insertion is best random. The other approach is to administer active drug in all attacks in most patients but let some patients treat with both active drugs and placebo. 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 (50) and recently another design with four attacks treated was used (67). 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: An easy-to-use, paper-and-pencil report form or an electronic diary that captures all predefined endpoints 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 study participants to fill out during migraine attacks. Sometimes, algorithms that ensure that the treated headache is a migraine attack can be, and have been, used successfully (e.g. (68,69)). Familiarization with data capture on the diary is important, and two approaches are useful. In one, participants complete the diary report for an attack while treating with their usual medication prior to being entered into the study and the form is reviewed. In the other approach, participants are asked to complete the diary at the randomization visit by recalling events of their most recent attack. The latter procedure is preferable because it minimizes delays in study participation.

1.3.2 Percentage of patients pain-free at 2 h Recommendations: The percentage of study participants whose headache pain score is zero at 2 h (pain freedom at 2 h), before any rescue medication should usually be the primary measure of efficacy and is recommended for both migraine with and migraine with aura RCTs.

Comments: Freedom from pain before use of rescue medication is simple, clinically relevant, reflects patients' expectations (70,71) is independent of the potential effect of other interfering therapies (e.g. rescue medication). It may be argued that some medications have a slow time to maximum (t_{max}) or time to effective (t_{eff}) plasma concentration and therefore an expectation of pain resolution within 2 h seems unrealistic. This is counterbalanced by the ethical argument that participants in clinical research should not be subjected to undue harm (the principle of non-maleficence) and the availability of effective drugs should not be delayed, that is, past 2 h.

Pain freedom at 2 h is one primary efficacy outcome measure, but it is not the only one. Pain freedom at a time point earlier than 2 h should be considered for parenteral (e.g. intravenous, intramuscular, subcutaneous) test drugs.

The primary efficacy outcome of pain relief at 2 h (headache response, that is, improvement of headache pain from moderate to severe at baseline to mild or none at 2 h) has been used extensively in several acute migraine RCTs (2–4,7,8), partly based on clinical experience suggesting that a patient perceives 'cure' while some residual headache may persist (8), and also because headache relief is statistically more powerful than the IHS recommended criterion (72). The validity of the clinical argument has been challenged severely as studies have shown that patients (a) do not consider it success to have a reduction in headache pain from moderate to mild (73), and (b) expect freedom from pain when treated (70,71).

Also, headache response assumes that the magnitude of change from severe pain to no pain is clinically equivalent to that of a change from moderate pain to mild pain, which is false (74). Finally, the ordinal pain scale of severe (pain score = 3), moderate (score = 2), mild (score = 1) and none (score = 0) assumes that pain severity is an interval variable, that is, that there is equivalence between score intervals. This assumption is not clinically validated.

1.3.3 Incidence of relapse (recurrence). Recommendations: After 2-h pain freedom, any headache pain from 2 to 48 h after study drug administration, regardless of its severity, should be considered a relapse or recurrence (the latter is a previously used term). Relapse is a secondary treatment failure. Relapse rates should not be compared across studies, and it is recommended to evaluate the differential rates of relapse in comparative RCTs only when primary efficacy rates are similar (75).

Comments: Relapse and recurrence are a major problem with all effective migraine treatments (7,49) and should be recorded as an important efficacy index. The reported incidence of recurrence as previously defined varies considerably, for example from 6% to 44% of initial responders for oral sumatriptan (7) and will most likely vary similarly with the currently suggested definition of relapse. Recurrence or relapse has been defined previously as occurring when a study participant initially obtains pain relief (improvement

from moderate or severe pain at baseline to mild or no pain at the primary efficacy time point) and subsequently experiences a moderate or severe headache, from the time point of primary efficacy and up to 24 h (49). This former definition of recurrence arbitrarily assumes, without a scientific or clinical rationale, that a mild recurrent headache is not a treatment failure. 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 (75).

1.3.4 Sustained pain freedom. Recommendations: The sustained pain freedom rate is defined as the percentage of study participants who are pain-free at 2 h with no use of rescue medication or relapse (recurrence) within the subsequent 46 h. Sustained pain freedom is a recommended secondary efficacy measure.

Comments: Sustained pain freedom is the ideal migraine treatment response and should be the ultimate goal in drug development.

However, the clinical success of many drugs could be underestimated when using this narrowly defined efficacy outcome measure. Indeed, the rates of sustained pain freedom for triptans have been only 15–25% of attacks treated (76), which could falsely suggest a relatively modest clinical efficacy.

Sustained pain freedom rates have been useful in comparing triptan efficacies (76), and it can be used for non-triptan comparisons.

The sustained pain freedom rate, by integrating initial response, no use of escape medication and no relapse (75,77), is a more scientifically robust outcome measure than relapse rates. Therefore, it is the recommended measure over relapse rate in comparative RCTs (78).

Sustained response rate is a composite efficacy outcome measure, based on similar concepts as those of sustained pain freedom rates. It is defined as headache response (not headache pain freedom) and absence of recurrence or use of rescue medication post-response (79). Sustained response is not recommended as a secondary efficacy outcome measure.

1.3.5 Total migraine freedom. Recommendations: The absence of pain, nausea, photophobia and phonophobia at the primary efficacy time point, that is, 2 h under most circumstances, is defined as total migraine freedom at 2 h, and can be used as a secondary efficacy measure.

Comments: Total migraine freedom is a combined efficacy measure that addresses pain and associated symptoms, and could satisfy the United States Food and Drug Administration (FDA) requirement to demonstrate efficacy of anti-migraine agents on each of at least four co-primary endpoints, namely pain relief (or freedom), absence of photophobia, absence of phonophobia and absence of nausea. Total migraine freedom was assessed post hoc from pooled data of the rizatriptan clinical drug development programme, and it was found to be 35% for rizatriptan vs. 8% for placebo (80). The total-migraine-freedom combined outcome measure is up to four times more powerful statistically than the strategy of four separate co-primaries because the majority of migraineurs do not show all associated symptoms and because these endpoints are not necessarily independent (80).

1.3.6 Intensity of headache. Recommendations:

a. The intensity of headache should be noted by participants just before the intake of study medication and at each subsequent pre-specified time point.
b. Headache pain intensity should be measured on a four-point scale where 0 = no headache; 1 = mild headache; 2 = moderate headache; 3 = severe headache. Alternatively, visual analogue scales can be used.
c. Headache intensity at the primary efficacy time point (e.g. 2 h), and before any rescue medication use, is critical for the analysis of the 2 h pain freedom primary efficacy outcome measure.

Comments: Pain Intensity Difference (PID) and Sum of Pain Intensity Differences (SPID), widely used in non-headache pain RCTs (81,82), have not been commonplace in acute migraine trials (83,84). In one analysis of four rizatriptan RCTs, SPID analysis was no more advantageous than the 2 h pain freedom analysis (85). PID and SPID assume a linear pain scale, that is, that a change from severe to moderate headache is equivalent to a change from moderate to mild headache. This assumption awaits scientific validation in migraine. Until then, and in order to allow comparison with results in other migraine RCTs, PID and SPID can be used as secondary outcomes, and pain-free response should remain a primary outcome measure.

1.3.7 Headache relief (headache response). Recommendations: Headache relief rate (or headache response (8)), that is, the 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. A time point before 2 h can be used when testing parenteral drugs.

Comments: Headache relief should still be used as an outcome measure, mainly to facilitate comparison of results in new randomized clinical trial (RCTs) with those of previous trial programmes (2–5,7,10,11,49,76).

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

Comments: Meaningful relief is subjectively assessed. In general, study participants measure time to meaningful relief using a stop watch (86–88). This method improves the precision of time estimates over fixed interval assessments commonly used in migraine trials. Strength of this method is that it captures and summarizes information about treatment response over a clinically relevant period of time instead of a pre-specified point in time (2 h). Also, time to meaningful relief can be assessed by powerful statistical methods such as survival analysis (86,87,89), which is superior to analyses using fixed time intervals (Planchard).

1.3.9 Time to pain freedom. Recommendations: Speed of onset of therapeutic effect can be evaluated using a survival analysis of pain freedom at time points earlier than 2 h. Time to pain freedom is a recommended secondary efficacy outcome measure.

Comments: Time to pain freedom is a more exact and less subjective measure than time to meaningful relief. Therefore, time to pain freedom should be the focus of time-to-event analysis in future RCTs.

The process of rating headache intensity at predefined time points earlier than 2 h (e.g. at 10–15 min intervals) can be used to analyse the speed of onset of drug response. Investigators should be aware that such additional data recordings can complicate headache diaries and potentially lead to missing data.

Time-to-event (i.e. to no headache when pain freedom is the outcome, or mild or no headache when pain relief is the outcome) analysis is the most appropriate statistical method to assess speed of onset of therapeutic effect. The difference between two treatments should be expressed as a percentage, and 95% confidence intervals (CI) should be given in order to better inform the reader about the significance of the difference. P-value calculations alone can be misleading.

Time-to-headache relief analysis has been used in the past (84,90,91), indicating that early response rates are relatively small, and perhaps clinically insignificant; subcutaneous sumatriptan is the exception (7,89,92).

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

Comments: The duration of an attack in migraine RCT is not only influenced by the effect of study drug, but also by physiological factors such as sleep and external variables such as use of rescue of medications beyond 2 h. These variables cannot be controlled for and therefore would not allow an accurate and scientifically sound interpretation of the independent effect of an investigational intervention on the migraine attack. The robustness of the pain freedom primary outcome measure and the pre-specified sustained pain freedom outcome mitigate the need for using attack duration as an efficacy measure.

1.3.11 Rescue medication. Recommendations: The percentage of patients taking rescue medication 2 h (or earlier if the time point for the primary outcome measure is specified at a time earlier than 2 h) after the intake of the test drug can be used as a secondary efficacy measure.

Comments: Theoretically, use of rescue medication at the primary efficacy time point reflects the participant's judgement of the efficacy of the test drug, although participants may use a rescue medication for conditions other than headache relief (e.g. anxiety, sleep). Rates of rescue medications have been found equally sensitive to 2 h pain freedom rates in some RCTs (54,93,94) but not in others (84).

The use of rescue medication should not be postponed beyond 2 h, or perhaps 1 h in paediatric trials and in trials where the primary time point for efficacy is at hour one post study drug administration, Allowing rescue medication at or beyond 4 h from the time of study drug administration was used previously (95) but is strongly discouraged.

1.3.12 Global evaluation of medication. Recommendations:

a. Global impression of study drug effect can be used as a secondary outcome measure.
b. A simple Likert-type verbal scale is recommended (e.g. very poor, poor, no opinion, good, very good).
c. Investigator's impression of study drug effect should not be used.

Comments: Participant's global impression of change (GIC) from baseline (global impression of investigational drug effect) is one of most clinically relevant outcomes because it is a composite assessment of study drug effects – on headache and associated symptoms – and adverse events, (tolerability). Several scales have been used to assess GIC in migraine RCTs (96–98).

GIC cannot be an efficacy outcome measure because it combines both efficacy and tolerability variables. GIC is recommended for use in phase III and IV trials and in comparative RCTs of two or more active study drugs.

1.3.13 Global impact (disability and quality of life). Recommendations:

a. Functional disability scores are important secondary global assessment endpoints.
b. Functional disability just before study drug administration and up to 2 h later, before any rescue

medication, should be assessed using simple ordinal, numerical scales such as: 0 = no disability (i.e. able to function normally); 1 = mild disability (i.e. able to perform all activities of daily living but with some difficulty); 2 = moderate disability (i.e. unable to perform certain activities of daily living); 3 = severe disability (i.e. unable to perform most to all activities of daily living, or requiring bed rest).

Comments: Disability scales are important global measures of study drug effects and side effects. They provide an assessment of the impact of an investigational drug on headache and associated symptoms and take into account adverse drug effects. Several global impact assessments have been used in migraine RCTs (54,84,93,94); for a comprehensive review see (99).

Some of these tools relate to disability assessments (e.g. Migraine Disability Assessment (MIDAS)), others address global impact (e.g. Headache Impact Test (HIT-6), Minor Symptoms Evaluation Profile (MSEP)), while others are best described as quality of life measures (e.g. 24 h migraine-specific quality of life measure (24-h MSQoL)). The 24-h MSQoL and MSEP are well suited for assessing study drug impact in acute migraine RCTs, but the others are more applicable to migraine prevention RCTs.

1.3.14 Migraine-associated symptoms: nausea. Recommendations: Presence or absence of nausea should be recorded at baseline, before study drug administration and at the time of assessment of the primary efficacy outcome (e.g. 2 h).

Comments: Nausea and vomiting are important associated symptoms of the migraine attacks (37) and drugs used for migraine treatment should also be demonstrated to be effective against these symptoms. Also, nausea and/or vomiting can complicate treatment as adverse events, and therefore these variables should be recorded at least up to 24 h. The interpretation of nausea or vomiting data should consider (a) drug efficacy effect; (b) drug-induced adverse effect (i.e. treatment-emergent nausea or vomiting); and rescue medication related nausea or vomiting when applicable. Finally, it is important to rate the severity of nausea in RCTs that include anti-emetics, either alone or in combination with other treatments. A simple 4-point categorical verbal/numerical scale (i.e. 0 = none, 1 = mild, 2 = moderate, 3 = severe) can be and has been used (35,48,100).

1.3.15 Migraine-associated symptoms: photophobia. Recommendations: Presence or absence of photophobia should be recorded at baseline, before study drug administration, and at the time of assessment of the primary efficacy outcome (e.g. 2 h).

Comments: Photophobia is very commonly associated with acute migraine attacks and can be disabling. Similar to nausea and phonophobia, the effect of an acute anti-migraine drug on photophobia should be evaluated in RCTs. A simple assessment such as presence or absence of photophobia is practical, although ordinal scales of severity can be used (e.g. 4-point scale where 0 = none, 1 = mild, 2 = moderate, 3 = severe) (100).

1.3.16 Migraine-associated symptoms: phonophobia. Recommendations: (a) Presence or absence of phonophobia should be recorded at baseline, before study drug administration, and at the time of assessment of the primary efficacy outcome (e.g. 2 h).

Comments: Migraine-associated phonophobia can be somewhat disabling. Similar to nausea and photophobia, the effect of an acute anti-migraine drug on phonophobia should be evaluated in RCTs. A simple assessment such as presence or absence of phonophobia is practical, although ordinal scales of severity can be used (e.g. a 4-point scale where 0 = none, 1 = mild, 2 = moderate and 3 = severe) (100).

1.3.17 Adverse events. Recommendations:

a. Adverse events (AEs) during treatment should be recorded contemporaneously in the study diary.
b. Spontaneous, or real-time or synchronous reporting is recommended and should be supplemented by responses to open questions when appropriate.
c. Characteristics of AEs that should be recorded at minimum, and which should conform to ICH-International Conference on Harmonization Good Clinical Practice (ICH-GCP) Guidelines, are:

1. event severity (mild, moderate, severe);
2. event seriousness (serious, non-serious);
3. times of onset; and
4. time of resolution (101,102).

Comments: Adverse events that occur during RCTs may or may not be related to study drugs (25). Adverse events should be recorded openly (i.e. spontaneously) without a priori biases in order to detect any unexpected effects that are observed during a drug development programme. The use of real-time or synchronous recording of AEs mitigates problems of recall. Finally, investigators are advised to determine whether or not an AE is believed to be drug-related.

The recording of AEs should adhere to the nomenclature and hierarchy of the Multilingual

European DOI Registration Agency (MeDRA: http://www.medra.org). Also, the reporting of AEs should be based on published IHS guidelines (103).

Reports of AEs should include, at minimum, the following for each study treatment arm:

1. Number of participants with one or more AE;
2. Number of participants with any serious AE, and details of each serious AE including causation;
3. Number of participants who withdrew from a study because of AE(s);
4. Number of participants with individual, pre-specified AEs – based on a priori knowledge, if any, of drug or drug class tolerability profiles;
5. Severity of specific AEs; and
6. Detailed table of individual AEs.

Detailed tabulation of all AEs by organ system is recommended instead of only listing AEs occurring in a pre-specified percentage of participants (commonly 3–5% and above). Also, it is discouraged to list only AEs whose frequency is statistically different from another treatment arm. Finally, it is worth noting that many regulatory authorities require additional details of AEs beyond those aforementioned (101,102). The chi-squared test and Fisher' exact test are commonly used for analysis of AEs.

1.3.18 Preference to treatment. Recommendations: Participants' preference to treatment is a useful exploratory and hypothesis-generating global assessment method that is best suited for crossover trials.

Comments: Preference is a subjective assessment that considers drug benefits and tolerability factors (104). In crossover RCTs, study participants can assess the benefit/tolerability ratios of different drugs or doses by giving their preference for different treatments (51). Recently published RCTs judged participants' preference on a 5-point Likert scale (105,106). Preference has not been assessed in some crossover RCTs (84,107).

To date, reported preference analyses in RCTs of acute migraine have been difficult to interpret because of the heterogeneity in participants' assessment of the balance between benefits and tolerability issues. Indeed, some patients prefer a more effective drug or dose at the expense of more adverse events, if relatively transient and mild (7,49), but others do not.

1.3.19 Treatment of relapse as an efficacy measure. Recommendations: The efficacy measure for treatment of headache relapse should be the percentage of patients pain-free within 2 h of headache relapse treatment administration.

Comments: Relapse of any severity of headache can be treated with active drugs or placebo in a randomized double-blind clinical trial. Reports to date indicate that the efficacy – as measured by the pain relief criterion – of certain anti-migraine drugs, the triptans, is similar regardless whether the treatment is for the primary or relapse headache (7,58,91).

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 properly calculate a sample size, investigators need to do the following at minimum:

a. estimate placebo response rates for the primary outcome measure, based on well founded assumptions;
b. define a clinically relevant difference between active and placebo response rates for the primary outcome measure;
c. establish the a priori statistical errors (α and β); and
d. determine an acceptable study power ($1-\beta$) (23).

Standard statistical methods can also be used for analysis of assessment measures in both crossover and parallel-group trials. Confidence intervals for differences between an active drug and placebo and between two active drugs (108) are strongly recommended in order to inform the reader more fully of the meaning of the results of the trial (109). A statement that two drugs are equipotent without giving confidence intervals is unacceptable. Time-to-event (pain freedom) analysis (90) or time-to-meaningful-relief analysis (86,89) 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 features and a high placebo effect invalidate open and single-blind trials of any prophylactic intervention. Clinical observations (e.g. (110)) and open trials may be hypothesis-generating and help to perform proper power calculations for placebo-controlled trials but a possible prophylactic effect in migraine has to be evaluated by double-blind, randomized, controlled trials. In these trials the novel intervention (drug) should be compared with placebo or no treatment. 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 at least two properly powered studies.

In most past trials comparing two active drugs, they have not been found to be statistically different. The numbers of patients needed to be recruited (see section 2.1) may require multi-centre trials, even in crossover trials (28). It is unethical to pursue a clinical trial in which the statistical power is too low to enable a fair evaluation.

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, regression to the mean or amelioration due to the passage of time (26). Therefore, comparative trials should also always be placebo-controlled.

The numbers of patients needed (see section 2.4) even in crossover trials may require multi-centre trials. If enough patients cannot be recruited it is better to avoid doing comparative trials with a low power. EL: This seems obvious. Do we need to mention it? As mentioned in the section on evaluation of results (section 2.3), in the planning phase only a few measures should be defined as the primary endpoint and these should be used in the power calculation.

2.1 Patient selection

2.1.1 Migraine definition. Recommendations: The diagnosis of migraine should be based on the ICHD-II (37).

Comments: The diagnostic criteria of the ICHD-II (37) are valid, reproducible and universally endorsed. Adopting the ICHD-II in RCTs ensures population homogeneity and allows for better interpretation of data both within and across clinical trials. Admittedly, many patients in clinical practice do not meet all ICHD-II criteria for migraine (i.e. probable migraine) and yet respond to conventional anti-migraine drugs (111). These observations underscore the fact that operational, symptoms-based criteria are not fully specific. Nonetheless, they remain the gold standard for participant entry criteria in clinical research. Furthermore, it is best to establish drug effect in a relatively homogeneous population before exploring other, more heterogeneous population targets. Lastly, it can be argued that strict adherence to the ICHD-II criteria for migraine only precludes a relatively small patient group.

In phase I and II migraine with aura and migraine without aura patients should be separated. If both forms are studied concomitantly in a RCT efficacy in a subform may not be detected (112,113). If a drug is developed specifically, such as tonabersat for migraine with aura, for one of the two subforms of migraine it should be studied further in phase III for this subform (concerning migraine with aura, see section 3.1).

It is not necessary to require that a certain percentage of attacks must be with aura. The aura can easily and specifically be diagnosed using an appropriate diary (112). Therefore it is only the number of attacks with auras that counts in the decision to include or not include a patient (see section 3.1 for trials in migraine with aura). With regard to migraine without aura, it is suggested that one should request that patients have only migraine without aura. These are the great majority of migraine patients and not difficult to recruit. In later studies, in late phase III and phase IV, patients with both types of migraine attacks may be included to make the study more naturalistic. Nevertheless, during the trial, each attack should be classified according to the IHS criteria according to clinical features (aura) captured on a diary card. When participants use symptomatic treatment (e.g. migraine-specific drugs such as triptans) all diagnostic criteria for a migraine attack without aura may not be fulfilled. For rules for migraine days see 2.3.2). Regarding the separation of migraine without aura and tension-type headache, investigators should consult the ICHD-II criteria (37).

2.1.2 Other (non-migrainous) headaches. Recommendations:

a. Early safety and efficacy studies should exclude participants with other headaches.
b. In later trials, participants with other headaches in addition to migraine should not be excluded from study participations if they clearly can differentiate between both types by pain quality and/or by associated symptoms.

Comments: Many patients with migraine have other types, non-migrainous headaches which do not meet IHS criteria for migraine (37). For the purpose of migraine clinical trials research, such headaches are called non-target or interval headaches.

Clinical experience suggests that many non-migrainous headaches in a migraine population are indeed 'form fruste' versions of migraine without aura, which would argue for their inclusion as target headaches. However, these clinical observations have not been fully and scientifically confirmed. Therefore, the exclusion of non-target headaches from migraine RCTs strengthens the scientific robustness of clinical trials designed specifically to address drug effects on the migraine condition.

2.1.3 Frequency of attacks. Recommendations: Attacks of migraine should occur 2–8 times per

month (or 4 weeks) with less than 15 headache 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 2–8 attacks per month allows for more rigid standards in certain trials. Other (including non-target) 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). For recommendations for trials in participants with chronic migraine with $\geq$ 15 headache day per month, see (38).

2.1.4 Duration of disease. Recommendations: Migraine should have been present for at least 1 year prior to entering into the study.

Comments: The 1 year requirement helps in excluding probable migraine and secondary headaches with features of migraine. Furthermore, at least a 1 year course of established migraine improves study population homogeneity.

2.1.5 Duration of observation. Recommendations: There should be a 3-month retrospective history and a prospective baseline of at least 1 month.

Comments: A 3 month retrospective history provides some assurance of the stability of migraine frequency prior to enrolment. This would be confirmed prospectively in a 1 month baseline period. The 1 month prospective period provides more accurate data on migraine frequency than the 3 month retrospective period, because it mitigates recall bias and allows for a regression to the mean prior to enrolment. 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.

The frequency of attacks of migraine with aura fluctuates much more than that of migraine with aura. Therefore a 1 month prospective run-in period must exclude patients who fail to have sufficient number of attacks. For this, only the 3 months retrospective period be used.

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

Comments: Migraine is not uncommon in the elderly with a prevalence range of 3–18% (40,114,115), but migraine with onset after 50 years is rare, approximately 2% (116).

Also, there is increasing uncertainty in the diagnosis of true migraine after age 50 years because the prevalence of secondary headaches with migraine features (e.g. ischemic stroke) increases. Therefore, it is prudent in RCTs of migraine to exclude participants with migraine onset after 50 years. This cautionary requirement does not unduly exclude many participants and, therefore, has minimal practical implications on participant recruitment.

2.1.7 Age at entry. Recommendations: Participants between 18 and 65 years of age are eligible for inclusion in adult migraine RCTs.

Comments: The study of drug effectiveness in paediatric (see 3.5) (39) and elderly migraineurs requires special protocols. These studies should account for, among other things, the different characteristics of paediatric migraine, clinical research ethical principles relating to elderly and paediatric populations, drug-drug interactions and co-morbidities, which are more problematic in the elderly population.

2.1.8 Gender. Recommendations: Both male and female participants should be included in migraine prevention RCTs.

Comments: Migraine is at least three times as common in women as it is in men (40–42). The higher prevalence of migraine in women is even more pronounced in clinical research for different reasons, including among others the higher consultation rates for migraine among women. This gender selection bias should be avoided by methods geared at recruiting men into migraine RCTs.

Appropriate precautions should be exercised when enrolling into RCTs women of child bearing potential and lactating women. Potentially fertile and sexually active women who do not practise adequate contraception should not participate in migraine preventive RCTs.

Menstrual migraine is discussed in section 3.6.

2.1.9 Concomitant drug use. Recommendations: Appropriate acute therapy must be allowed for individual attacks and has to be documented (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 (except contraceptive drugs). In later trials 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 meet ICHD-II criteria for medication overuse (37); 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 (117)); 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 tranquilizer 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 new 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 antimigraine drugs may unfairly bias the study. However, prior 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, as criteria for 'refractory migraine' are not universally available. We suggest that the patients should not have failed on more than two prophylactic agents.

2.1.10 Co-morbidity. Recommendations: Patients with certain co-morbid medical conditions may need to be excluded from some migraine trials. For all trials, medical conditions that exclude potential participants must be specified and specifically screened for when evaluating a potential participant.

Comment: Specific co-morbid medical conditions that exclude potential participants from participation in migraine trials may differ among trials according to the therapy under investigation. Commonly, although not necessarily universally, excluded conditions include other acute or chronic pain disorders, severe psychiatric disease, infections, malignancy, short life expectancy, cardiovascular disease, cerebrovascular disease, uncontrolled hypertension, degenerative central nervous system diseases and others. Other disorders may exclude potential participants from migraine studies depending upon the mechanism of action and side effects of the study treatment. Pregnant and lactating women are typically excluded from migraine trials unless that is the intended population.

2.2 Trial design

2.2.1 Blinding. Recommendations: Randomized controlled trials in migraine prophylaxis should be double blind.

Comments: Migraine symptoms are defined subjectively. Therefore, efficacy outcomes have to be assessed in ways that minimize bias, and blinding to treatment intervention is one acceptable and recommended approach. Open-label and single-blind trials cannot mitigate bias and therefore are not recommended. That said, long-term safety trials and naturalistic trials do not need to be blinded.

Triple blinding, that is, participant-blind, investigator-blind and sponsor-blind (statistician or other personnel evaluating the study results), may be beneficial when data evaluation can introduce an undue bias on study results.

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 (assay sensitivity) of the trial, which would allow better generalizability of study results.

Comments: There is overwhelming evidence that migraineurs, similar to people with pain disorders, respond positively or negatively to placebo (placebo effect or response). Various studies have demonstrated that the placebo response rates (e.g. reduction in migraine frequency or 50% responder rate) in migraine prophylaxis usually range between 20% and 40%, or even higher (e.g. (118)). Therefore, the true drug effect cannot be established unless one can control for the placebo response. Also, the absence of a placebo arm in active-drug comparative trials does not allow a clear interpretation of active-drug effect, or lack thereof. For example, if two active drugs are found equally effective in a non-placebo-controlled comparator trial, using conventional frequentist (as opposed to Bayesian) statistical approaches, the effect of either or both could simply be placebo-related. Finally, the use of a non-contemporaneous placebo arm, that is, the use of historical placebo data, is not valid scientifically and is highly discouraged in clinical research.

2.2.3 Parallel-group and crossover designs. Recommendations: Either crossover or parallel-group design can be used, depending on the trial's specific objectives and particular drug under study.

Comments: The advantage of the crossover design is that it is approximately eight times more powerful than

the parallel-groups design in prophylactic migraine trials (119). Higher study power translates into lower participant sample size, which has the advantage of exposing fewer participants to investigative drugs. However, it should be noted that the eight-times higher power is not universally true as certain parallel-group design studies have required only two to four times the number required in a crossover design (120); for further discussion see (121).

The 'power advantage' of the crossover design is countered by several drawbacks, including:

1. requirements for a prolonged trial duration from the incorporation of at least two study periods and from extended washout periods;
2. likelihood of higher dropout rates secondary to the prolonged trial duration, resulting in loss of statistical power;
3. differential adverse events that could potentially unmask the blinding during a treatment period;
4. ethical dilemmas of switching participants to the alternative treatment – either placebo or active drug – when they have experienced benefit during the initial trial period;
5. possibility of a carryover effect.

The latter drawback can be mitigated with appropriate statistical techniques (26), although even this approach is criticized (122). It has been stated that crossover design trials are not well suited for conditions with fluctuating course during study periods (123). However, this fluctuation of migraine will also be a problem in a parallel-group design.

2.2.4 Randomization. Recommendations:

a. Patients should be randomized in relatively small blocks both in crossover and parallel-groups trials.
b. Randomization should occur after the run-in (baseline) period.
c. The Latin square method should be used for triple crossover designs (e.g. two active drugs and placebo).
d. Type of randomization should be clearly defined in the study protocol, under the statistical analysis plan, and accurately reported (e.g. publication, post-study synopsis or full report).

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

2.2.5 Stratification. Recommendations: Participant stratification by baseline migraine characteristics that probably influence efficacy outcomes (e.g. frequency of attacks: < 3 or ≥ 3 attacks per 4 weeks) is recommended in parallel-groups trials. Stratification is not necessary in crossover trials.

Comments: Randomization alone may not ensure full comparability between participants in different treatment groups, and stratified randomization is sometimes used to circumvent potential imbalances between treatment groups. According to the European Agency for Evaluation of Medicinal Products, 'stratification variables, regardless of their prognostic values, should usually be included as covariates in the [study] primary analysis.' Furthermore, stratification by important prognostic factors should be limited to only a few, and only to those that historically have a clearly demonstrated impact on the primary study outcome.

Baseline migraine characteristics that affect efficacy outcomes in migraine prevention remain elusive. The exception may be baseline migraine attacks frequency (124). Therefore, it is reasonable to use frequency of attacks as a basis for stratification and in order to assure baseline comparability, especially because attack frequency is a principal outcome measure in migraine prevention RCTs.

2.2.6 Baseline (run-in) period. Recommendations: A 1 month baseline run-in period is recommended.

Comments: During the baseline run-in observation period placebo is discouraged.

Although 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 discouraged. 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:

a. Treatment periods of at no less than 3 months in phase II RCTs and up to 6 months in phase III trials should be used.
b. A 4 week post trial observation period is highly desirable.

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. Such benefits outweigh the potential

risks of dropouts, which would lead to reduction in the study's statistical power.

2.2.8 Washout periods in crossover trials. Recommendations: In crossover trials a washout period of 1 month should be used.

Comments: The benefits of treatment may persist even after treatment is withdrawn during prophylactic drugs trials, and some authors advocate using long washout periods without resorting to statistical techniques that deal with carryover effect (125). Therefore, allowing sufficient time for a complete disappearance of study drug effect between treatment periods in crossover trials is critical. This drug-free (placebo, regardless of treatment sequence) period must exceed the time it takes for full pharmacokinetic and pharmacodynamic eliminations. Complete or near complete drug pharmacokinetic elimination is typically 5–7 elimination half-lives but drug pharmacodynamic disappearance time is often unknown. It is reasonable to consider 1 month as a practical and feasible washout period.

2.2.9 Dosage. Recommendations:

a. The widest possible dose range should be tested in migraine prevention RCTs.
b. The no-effect dose and the maximum tolerated dose should both be established.

Comments: The putative pharmacological mechanism of anti-migraine drugs is largely elusive, and no dose assumptions could be made based on pre-clinical pharmacological activity. Therefore, the choice of doses in trials remains empirical, albeit critical, and should be based on the range of tolerated and safe doses that has been determined in early clinical pharmacology trials. Failure to explore a wide dose range potentially leads to suboptimal dosing in phase III programmes, which can result in inaccurate conclusions on efficacy. Alternatively, use of high doses in early trials could lead to tolerability issues resulting in early programme termination.

Attempts should be made to evaluate drug-response curves early in the clinical drug development programme in order to better gauge optimal dosing in phase III trials. Unfortunately, such relationships have not been established with existing migraine prevention pharmacotherapies (e.g. propranolol, valproate), with the exception of topiramate (126).

Drug dosages in early efficacy trials (e.g. phase IIa) can be guided by the investigational plasma levels. The recommended approach to evaluating concentration-response curves, and the related dose-response curves, is to obtain blood levels in close temporal proximity to the recording of the effect (efficacy and tolerability) measures. Also, information on blood levels can assist in evaluating compliance.

Similar to trials of a single agent, RCTs that compare two or more active drugs should use optimal and comparable doses in order to establish equivalence, superiority or inferiority. Until valid scientific data are generated on dose effect, the choice of doses in comparative trials remains based on rational clinical judgement, which should be clearly articulated and defended prior to initiating any trial.

2.2.10 Symptomatic (acute) treatment. Recommendations:

a. Participants should use and accurately report their usual symptomatic or acute treatment, provided that it can be administered safely with the study medication.
b. Changes to symptomatic treatment regimens during the conduct of the trial should be kept to a minimum.

Comments: The optimal treatment for acute attacks in migraine prevention RCTs is both ethically and clinically indicated. Standardizing symptomatic treatment, which has been used previously, is desirable but impractical, and may not be the optimal treatment for some of the enrolled participants.

Overuse of analgesics, ergotamine or triptans is not allowed in migraine prevention RCTs. For further details, see section 1.1.9.

2.2.11 Follow-up visits. Recommendations: Participants should be evaluated at least every 4 weeks, if study intervals are defined in weeks or monthly otherwise.

Comments: Regular follow-up visits are important aspects of migraine prevention RCTs to review diaries, monitor adverse events, ensure compliance and promote continued participation in the study. At minimum, visits every 4 weeks (or monthly) fulfil the aforementioned objectives and do not present undue stressors on trial logistics. Occasionally, more frequent visits may be required, in particular when certain potential AEs are being monitored (e.g. hepatic enzyme abnormalities).

2.2.12 Compliance. Recommendations:

a. Compliance with prophylactic medication in clinical trials should be promoted and stressed at baseline and at every visit thereafter.
b. Monitoring compliance in early clinical trials (e.g. proof-of-concept) is recommended.

Comments: Evidence of poor compliance with migraine prophylactic drugs is well established (127) and can be falsely interpreted as drug failure. Therefore, it is crucial to monitor drug compliance in migraine clinical research, particularly early in an investigational drug development programme, and this is best achieved through blood level assessments. Obtaining blood levels in phase III trials often is impractical and does not approximate naturalistic settings. Therefore, a more pragmatic approach to compliance monitoring is acceptable. One such approach is the drug or pill count at every follow-up visit, and repeated emphasis on the values of adherence to the protocol requirements. The emphasis on compliance to protocol requirements not only serves the purpose of adherence to the investigational drug regimen but also stresses proper completion of headache diaries (see below).

2.3 Evaluation of results

2.3.1 Headache diary (see also section 1.1.3).

Recommendations:

a. An easy-to-use, paper-and-pencil report form or an electronic diary that captures all predefined assessment measures (efficacy, tolerability and safety) should be used.
b. Real time diaries are strongly encouraged.
c. Complicated diaries are discouraged.

Comments: The headache diary should be designed to fully capture efficacy and tolerability measures that have been pre-defined for the particular study. Details of diary design are a local and regulatory matter, and are subject to the language, cultural and regulatory environments where studies are conducted. That said, multi-national trials should use consistent diaries in order to allow appropriate data interpretation across different trial sites. Investigators' evaluation of efficacy is not recommended.

Only observations that are relevant to the study's primary and secondary objectives should be included in headache diaries. The use of diaries that include a multitude of observations could lead to missing data and may overwhelm study participants, leading to poor compliance and difficulty in interpreting study results.

2.3.2 Primary efficacy measures.

Recommendations:

a. Two primary efficacy measures are recommended. They are:
b. Number of migraine attacks per evaluation interval;
c. Number of migraine days per evaluation interval.
d. Either 4 weeks or 1 month is considered an appropriate evaluation interval.
e. The frequency of migraine attacks, or migraine days, either during the entire treatment period or during the last treatment interval is compared with the baseline frequencies.

Comments: The number of migraine attacks should be recorded irrespective of their duration, and the following guidance should be used for distinguishing an attack of long duration from two attacks, or for distinguishing between attacks and recurrences:

a. A migraine attack that 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 should be considered one attack.
c. A practical solution to differentiating attacks using diary entries is to consider as distinct attacks only those that are separated by an entire 24 h period of freedom from headache. These suggested rules to distinguish between one and two attacks, while accounting for up to 48 h of relapse/recurrences, are arbitrary yet practical.

Some trials may permit the inclusion of participants with interval headaches, but only if they are able to differentiate between migraine and interval headache attacks. A simple instruction on the headache diary that would assist participants in correctly differentiating among headache attack types is as follows: 'Is the headache you are experiencing a true migraine or another type of headache? If it is a non-migraine, record when it started and when it ended.'

Accordingly, investigators analyse the non-migraine data by the number of days with such headache types. Difficulties with defining the duration of a migraine attack have led to proposing migraine days as an alternative and perhaps simpler efficacy endpoint (28). Migraine days are easier to record on headache diaries and may be very useful in large-scale, long-term, pragmatic trials. However, migraine days, unlike migraine attacks, represent a composite endpoint because it incorporates attack duration. Attack duration depends on acute (symptomatic) treatment of the migraine and the therapy for recurrence/relapse, if it occurs, and neither typically is standardized in migraine prevention RCTs (see earlier discussion). Therefore, it can be argued that the efficacy endpoint 'migraine days' is not as accurate (neither as sensitive nor as specific) as 'migraine attacks' when the primary study objective is the evaluation of a preventative agent. This lack of

accuracy of the 'migraine days' endpoint makes it a less desirable measure in early (phase II) trials that seek high specificity and study cohort homogeneity.

2.3.3 Intensity of headache (see section 1.3.6). Recommendations: A recommended numerical/verbal scale is appropriate for migraine prevention RCTs.

Comments: The main objective of RCTs for migraine prophylaxis is the reduction in attack frequency, and the use of abortive treatment is not standardized. Therefore, it is unnecessary to capture migraine pain severity at different time points during an attack. Simply recording the maximal pain intensity by means of a verbal scale (e.g. 0 = no headache; 1 = mild headache; 2 = moderate headache; 3 = severe headache) prior to taking symptomatic medication is sufficient. Visual analogue scales do no serve any meaningful objective during the conduct of a migraine prophylactic RCT.

2.3.4 Duration in hours. Recommendations:

a. Participants can be asked to record the times of onset and termination of each migraine.
b. Duration of a migraine attack is not a recommended efficacy measure in prophylactic trials.

Comments: Duration of attacks in migraine prevention RCTs is modified by acute treatment, which cannot be standardized among patients. Furthermore, the onset of a migraine cannot be established with certainty in participants who awaken with a headache. Lastly, some participants may fall asleep while in pain, and wake up without headache, which would create difficulty in accurately timing the end of an attack. For these reasons, migraine attack duration is not a valid endpoint in migraine prevention clinical trials, and can only be used in exploratory, hypothesis-generating analyses.

2.3.5 Drug consumption for symptomatic or acute treatment. Recommendations: Both the number of migraine days treated with abortive agents and the number of drug administrations for acute therapy should be recorded.

Comments: Consumption of drugs for symptomatic migraine attacks can be a pre-defined secondary efficacy measure. Simply, participants should be instructed to record in their headache diaries the times they used abortive therapy.

The use of drug consumption as secondary endpoints in crossover trials may be valuable. Its use, even as a secondary endpoint, is not recommended in parallel design studies.

2.3.6 Patients' preferences and satisfaction. Recommendations:

a. Patients' preference and satisfaction measures can be used as secondary global outcomes.
b. Patients' preference is best assessed in crossover design trials.

Comments: Patient preference or satisfaction measures are global outcomes that assess the overall experience with study drug, or treatment period (in case of crossover studies) in clinical trials. Preference and satisfaction are subjective, participant-defined, composite measures of efficacy, tolerability, safety and expectations. The value of such measures is most desirable in phase III and pragmatic (practical controlled) trials. Preference or satisfaction measures are best handled as secondary outcomes in migraine prevention RCTs.

A simple, 5-point, Likert-type scale (1 = very dissatisfied, 2 = somewhat dissatisfied; 3 = neither satisfied nor dissatisfied, 4 = somewhat satisfied, 5 = very satisfied) can be used to evaluate preference for, and satisfaction with, a study drug in migraine prevention RCTs.

Investigators should be cautious when designing studies that evaluate preference or satisfaction, particularly when participants have had previous experience with one or more of the treatment arms. Such scenarios could lead to participant's bias (128,129). When two drugs with similar adverse events are compared (e.g. two β-blockers), preference can be asked for in a three-way-crossover trial with placebo control (130).

2.3.7 Responder rate. Recommendations: The proportion of participants with ≥ 50% improvement in migraine attack frequency or ≥ 50% reduction in number of migraine days (i.e. responder rate), as compared to baseline values, is an important secondary efficacy outcome.

Comments: The choice of 50% or greater reduction is arbitrary yet clinically relevant as most patients with migraine value ≥ 50% improvement in headache frequency as the most important attribute of an effective migraine preventive drug (131).

The dichotomous outcome of '50% responder rate' is relatively insensitive to treatment effects, but can be used to identify subgroups of responders in post hoc analyses, and it may correspond to expectations of many patients. Findings from such analyses would need to be confirmed in prospective, enriched-design trials that enrol these cohorts, or groups with similar migraine characteristics. In other words, the '50% responder rate' analyses are useful hypothesis-generators for subsequent trials.

Responder rates are particularly vulnerable to selection bias, limiting the generalizability of a study that focuses on such an outcome. Responder rates can be used in meta-analyses of placebo-controlled RCTs (126,132). Alternatively, time series analysis (27,133) can be used in defining responders.

2.3.8 *Adverse events.* Recommendations:

a. Adverse events (AEs) during treatment should be recorded contemporaneously in the study diary.
b. Spontaneous, or real-time, or synchronous reporting is recommended and should be supplemented by responses to open questions when appropriate.
c. Characteristics of AEs that should be recorded at minimum, and which should conform to International Conference on Harmonisation Good Clinical Practice (ICH-GCP) Guidelines, are:

1. Event severity (mild, moderate, severe);
2. Event seriousness (serious, non-serious);
3. Times of onset; and
4. Time of resolution (101,102).

Comments (also see section 1.3.17): Adverse events tend to precede efficacy and, in clinical practice, represent a significant problem in prophylactic migraine treatment, often leading to treatment discontinuation. Therefore, the incidence of AEs, especially those resulting in discontinuation of treatment, is an important measure of the druggability (overall therapeutic acceptability) of an investigational agent for migraine prophylaxis. It should be noted that AEs may or may not be pharmacological side effects of study drug.

2.4 *Statistics*

Treatment arm comparisons in parallel-group studies can be made by evaluating differences in the primary efficacy measures (e.g. migraine frequency) during the last month of treatment or across all treatment periods. Alternatively, change from baseline in the primary efficacy endpoint can be compared among study treatment groups. The latter approach is conceivably more powerful, but analyses have so far shown only that this is marginally so (PT-H, personal observation). Regardless of the approach chosen, baseline values can be used as covariates in a multivariate analysis, but the results should be interpreted with caution (134).

Suitable statistical methods can be used in the cross-over design for correction for a period effect ('time effect'), if present (26,135). Here again, similar to statistical methods for acute trials (see section 1.4), confidence intervals for treatment differences are recommended in order to more fully interpret p-values and statistical differences (25). Also, statements that two drugs are comparable without giving confidence intervals are discouraged. Lastly, statistically significant differences (e.g. p-value < 0.05) in secondary outcomes measures should be used only as hypothesis generators. In other words, investigators are cautioned not to draw firm conclusions based on statistical differences in secondary outcomes.

Results of studies with several objectives and correlated primary outcomes should adjust for multiplicity. There are various methods of adjusting for multiplicity. The simplest and most conservative, Bonferroni adjustment, divides the p-value by the number of outcomes analysed. Fixed sequence methods use pre-defined criteria such as clinical relevance or statistical step-down approach (differences are judged insignificant as soon as the p-value exceeds a threshold, e.g. 0.05). A more flexible approach that possibly avoids arbitrary predefined fixed sequences is the flexible fixed sequence testing method.

It is critical to establish a statistical analysis plan before initiating a study in order to avoid any potential biases in data interpretations. The statistical analysis plan should have explicit details of the proposed analyses and data handling for all pre-defined primary and secondary outcomes. Post-hoc analyses are discouraged except for the purpoess of hypothesis generation.

Endpoints 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. Of increasing importance is the impact of clinical measures on patient-perceived quality of life, performance in daily activities (work and familial-social duties). For examples see (136–140).

3 Special comments

3.1 *Trials in migraine with aura*

Migraine with aura (MA) and migraine without aura (MO) are clinically two different entities (141) and the pathophysiological mechanisms leading to the onset of attack are most likely different (142). The headache phases, however, have in most cases similar headache features and similar associated symptoms and MA and MO might thus share some basic pain mechanisms.

For inclusion of participants in RCTs on these two subforms, see section 2.1.1.

So far no drug has been shown to be effective for migraine aura or subsequent headache. In two RCTs triptans, sumatriptan 100 mg and eletriptan 40 mg,

administered during the aura phase were without effect on either the aura or the headache phase (34,143).

The main problem in MA is the diagnostic accuracy. To this end special diagnostic and treatment diaries should be used (144). A 'blurred vision' is not enough to classify a migraine as MA (145). Detailed instructions of MA participants on how to fill out these diaries are essential.

The current IHS Classification (37) subdivides group 1.2.1 (migraine with a typical aura) into aura followed by migraine headache, aura followed by non-migraine headache and aura not followed by headache.

In RCTs migraine should for practical purposes be subdivided into:

1. migraine aura (MA) (without headache);
2. migraine with aura (any headache following aura); and
3. migraine without aura (MO).

It should be noted that many participants with MA also have MO attacks (146).

Most studies for both acute and preventive migraine treatment are carried out in mixed populations with MA, MO or both. Whether these two types of attacks occurring in the same patient respond similarly or differently to drugs is impossible to tell unless each attack is separately classified as MA or MO. The importance of this distinction was underlined in recent studies with tonabersat. Attacks of aura (with or without a headache) were statistically significantly reduced (112) whereas attacks of migraine with and without aura were not (113).

3.1.1 Drug trials dealing with acute treatment of MA. In trials evaluating the acute treatment of MA, it should be clearly stated whether the aim is to abort or reduce the length of the aura or to reduce or eliminate the headache, as these two are probably based on different neurobiology.

The MA patients should have a frequency of at least one aura or MA per month.

In trials where the aura is the focus of the study, the primary efficacy measure should be duration of the aura. The usual duration of the migraine aura should be at least 20 min (144). A detailed recording of each aura symptom and total duration of the aura is mandatory and should be based on uniform requirements. Only drugs with a very quick onset of action can be expected to influence the duration of the aura, for example an injected or an inhaled drug.

In trials where the expected effect of the treatment is to prevent the headache phase the number of headaches following the aura should be the primary efficacy measure. In addition, pain freedom after 2 h can be a secondary efficacy measure. When the focus is on headache prevention in MA, a feasible compromise can be that the aura is followed by headache in at least 80% of the attacks.

3.1.2 Drug trials dealing with prophylactic treatment of MA. Care must be used to ensure that participants can distinguish between aura, MA and MO and use an appropriate diary. Because MA patients with an attack frequency of at least one per month, the frequency recommended by Hauge et al. (144), are relatively rare, the crossover design has been recommended because of its superior power. In two prophylactic RCTs in MA carry-over and period effects have not been a problem (112,147). A baseline period is not recommended.

The primary efficacy measure should be the number of auras (144). Secondary outcome measures could be the number of migraine headache days and/or the number of days with any headache, and otherwise as for MO.

3.2 Early intervention trials

To facilitate migraine diagnosis and to minimize placebo response, participants have been required in the triptan clinical trials programme (7,8,78,148) to wait until headache is at least moderate to before taking study medication. This is not, however, the way in which many participants treat their migraine attacks in clinical practice. Accumulating evidence indicates that 'early intervention' with an oral triptan may be the most effective acute treatment strategy, leading to a higher percentages of pain-free responses at 2 h (43% for zolmitriptan 2.5 mg (149), 53% for almotriptan 12.5 mg (150), 58% for sumatriptan 100 mg (151) and 66% for rizatriptan 10 mg (152)) than the 'traditional' administration when pain is moderate/severe (153). We still do not know whether this advantage would be explained by a lack of central sensitization (154) or by a pure pharmacokinetic effect due to a normal absorption of drugs compared with a delayed absorption later in the established migraine attack (59,62). In one small ($n = 20$) prospective crossover study, however, early and late treatment with subcutaneous sumatriptan 6 mg had similar efficacy, indicating that central sensitization is not important for the response to a triptan (155).

3.2.1 Design of early intervention trials. It is important to note that published early intervention trials have been characterized by wide variations in methodology and design and important differences in terms of the definition of early intervention.

As time (how soon the treatment is taken after the migraine begins) and intensity (treatment is taken when the pain is still mild) are not necessarily interchangeable (136,156), the adequate definition of 'early intervention' in early intervention trials should be: 'treatment administration when both pain intensity is mild and within 1 h of headache onset'. According to this, participants with headaches predominantly occurring during the night or on waking in the morning and participants with more than one type of headache who are not able to differentiate migraine from other headaches should be excluded from early intervention trials.

The choice of design depends on the purpose of the RCT. It can be to show that early/mild treatment is more effective than late/moderate/severe treatment. In this case the theoretically ideal trial design for early intervention would be a multiple crossover trial in which the same participant treat four attacks (early intervention with placebo, early intervention with active, late intervention with placebo and late intervention with active) in randomized order (14). However, in practice the feasibility of such a trial seems very difficult. An acceptable design recommended by this committee is that used in a recent trial (150) with four parallel arms treating one attack: early intervention with placebo, early intervention with active, late intervention with placebo and late intervention with active (8). An intermediate alternative would be a two-arm parallel design in which patients treat two attacks, with one treatment arm allocated to early intervention and the other to late intervention; one of the two attacks would be treated with placebo and the other with active, in a randomized order (14).

If the purpose is to show that a drug is more effective than placebo when treating early in the mild phase (e.g. (149)) then traditional parallel group comparison or crossover design can be used (see 1.2.3).

The primary endpoint should be pain freedom at 2 h. A secondary efficacy measure could be sustained pain freedom from 2 to 48 (see 1.3.3). However, as the aim of these trials is also to analyse prevention of pain progression, sustained pain freedom (see 1.3.3) could a co-primary endpoint (14). The number of protocol violators (participants assigned to treat mild headache who treat moderate-severe and the reverse) in early intervention trials can be significant (150). As protocol violators, these participants could be excluded in the intention to treat analysis, but there is a risk in performing this analysis under the level of size of power calculation. An acceptable alternative is to reassign these participants to their actual treatment groups provided that this re-allocation is done before the blind is broken.

3.3 Health-related quality of life (ability to function in daily activities)

Endpoints currently used in migraine trials may not reflect all participants' values and are not appropriate to assess the global effect of treatments on patient-perceived sense of well-being and quality of performance in different roles and daily activities. Restoring the patient's ability to function as well as improving their quality of life are among the main objectives of migraine-specific therapies, according to international treatment guidelines (157–159).

In synthesis, the global impact of migraine can be measured considering disability or quality of life.

Disability can be defined as the complex of restrictions in ability to perform an activity in the manner or within the range considered normal for a human being, or as the sum of difficulties/impairment/decreased productivity in daily activities (160,161).

Quality of life, or, better, health-related quality of life (HRQOL), refers to the overall effect of illness and its therapy on a participant's perception of his or her ability to live a useful and fulfilling life, including physical and mental components, general health perception and level of performance/participation in different roles (162,163).

HRQOL can be measured with a variety of generic and specific (i.e. specifically developed to be used in participants affected by a specific disease) questionnaires. Generic questionnaires are more useful to compare different study populations with different diseases, whereas disease-specific questionnaires are specifically designed to assess HRQOL associated with a single disease or treatment, and are more likely to be sensitive to changes after specific treatment interventions.

Several questionnaires have been tested in interventional studies on migraine patients. Among the generic questionnaires, Minor Symptoms Evaluation Profile (MSEP) (164) and SF-36 (165) were used. Among the migraine specific questionnaires, the most used were Migraine-Specific Quality-of-Life Questionnaire (MSQ) (166–170) and the 24 h Migraine-Specific Quality Of Life Questionnaire (24 h MSQ) (171,172).

Disability induced by migraine can be measured with questionnaires developed and validated in headache/migraine patients with good psychometric properties, such as MIDAS (173–175), HDI (176) and HIT-6 (177–180).

These questionnaires differ in several characteristics: the time interval investigated (e.g. 3 months for MIDAS, 4 weeks for HIT-6 and SF-36, 24 h for the 24 h MSQ); the number of questions to be answered (e.g. six for HIT-6, seven for MIDAS, 14 for MSQ,

15 for the 24 h MSQ, 25 for HDI, 36 for SF-36); the numerical scores obtained (e.g. total scores for MIDAS and HIT-6, summary scores or scores for each different domain for SF-36 and MSQ).

Disability and HRQOL have been in fact included as endpoints in several clinical trials evaluating the outcome of migraine after treatment interventions, with both symptomatic and prophylactic compounds.

Investigators should be aware that SF-36, MSQ, HIT-6 and MIDAS have been found to be sensitive to clinical changes occurring after prophylactic treatments in various different open studies (136,181,182) and also in RCTs (137,139,183–185). SF-36 and MSQ were found to be able to demonstrate improvement following repetitive administration of triptans in open trials (186–188).

The 24 h MSQ has been found to be sensitive to clinical improvement in the hours immediately following a single triptan administration, both in open studies (189) and RCTs (190–192).

Besides the above-reported tools, SF-12 and WHO-DAS II are to be considered. SF-12 is a generic HRQOL that is an abbreviated version of SF-36, which exists in two versions, exploring HRQOL in the previous 4 weeks and in the previous week (193). WHO-DAS II (194) is a generic disability tool, in contrast with the above-reported disability tools, which were developed specifically for headache patients. WHODAS II has the advantage of being based on the biopsychosocial model endorsed by the World Health Organization with the International Classification of Functioning, Disability and Health (ICF) (160). In fact, the modern definition of disability emphasizes the importance of interaction, in an individual, between a health condition and the environmental factors in which that person lives, and is defined as a difficulty in functioning at the body, person or societal level, in one or more life domains. WHO-DAS II has been recently tested with success in migraine samples (195,196).

Recommendations:

The use of standardized, validated tools to assess the changes in ability to function and in HRQOL in clinical trials is recommended as secondary endpoints.

For trials with symptomatic drugs 24 h MSQ is suitable for assessing HRQOL during an individual attack, while MIDAS, HIT-6, HID, SF36, SF-12, WHO-DAS and MSQ could be used for changes in ability to function and HRQOL in those trials involving treatment periods during which repetitive attacks are to be treated.

For trials with prophylactic drugs symptomatic drugs MIDAS, HIT-6, HID, SF36, SF-12, MSQ and WHO-DAS can be used.

Investigators may choose the most appropriate tools on the basis of the design of the specific trial as well as taking into account the different characteristics of each tool (such as the domains investigated, the time interval assessed and the availability of validated versions in the language used by the enrolled patients).

Analysis of the change in total scores and/or in the scores at different domains or scales should be performed, reporting the differences between baseline and treatment periods and/or between active drug and placebo arms. The statistical methods used – or the parameters chosen to define a clinically meaningful change after acute or prophylactic treatments – should be clearly indicated in methods and accurately reported for each disability and HRQOL tool.

To limit confounding factors in disability and HRQOL scores, investigators are encouraged to instruct patients that their lifestyle (diet, sleep hygiene, exercise, etc.) and behavioural treatments (cognitive therapy, biofeedback, etc.) should remain consistent among treatment groups and across centres during the trial.

3.4 Sources of patients

Migraine sufferers attending speciality clinics and primary care facilities are eligible for enrolment in clinical trials as long as they meet trial study criteria. 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 participants produces a representative sample of migraineurs.

The enrolment of people who habitually participate in migraine clinical trials should be discouraged. Also, it is recommended that investigators establish a database of the number of migraine studies of any kind in which each particular patient has participated in the last 2 years.

Participation in earlier trials should be recorded and presented in the publication.

3.5 Trials in children and adolescents

3.5.1 Drug trials dealing with acute treatment.

Few randomized clinical trials of drugs for acute migraine have been performed in children or adolescents (197–207), 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 (199), 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 (208). It may be appropriate to select these, becasuse 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 (208). Adolescents on the other hand generally do not wish to sleep (208). Otherwise, in the absence of good experience the recommended primary efficacy endpoint is pain freedom 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 (208)).

3.5.2 Drug trials dealing with prophylactic treatment. In a meta-analysis of behavioural and prophylactic pharmacological intervention studies in paediatric migraine (209) 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 probably wise to use a simple headache diary and days with migraine as the primary efficacy measure. The limited experience available (210,211) 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).

3.6 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 (32) suggested that 'menstrual migraine' should be defined as migraine attacks occurring within day 1 plus or minus 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 (37) 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 (212), only 7% of female patients had pure menstrual migraine. One study on menstrual migraine suggested that 3 months of prospective diary information is needed to be certain of the diagnosis (213).

3.6.1 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 related 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 dairy 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 related 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 (section 1.3.2) but, in these often long-lasting migraine attacks with a high risk of relapse, sustained pain freedom (section 1.3.3) will be an interesting measure.

3.6.2 Drug trials dealing with prophylactic treatment. Standard methods may be used. 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 (214) to 48 h (215) 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 (216,217) designs can be used. Using the crossover design the efficacy of perimenstrual oestrogen supplementation has been demonstrated in three relatively small trials in pure menstrual migraine (215) and in menstrually associated migraine (218,219), illustrating the power of this design (for a review of these and other trials, see (220)). 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.

3.7 Publication of results

Publication of research is an ethical imperative (221). 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' (31). 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 (31): '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.' The publication should conform to generally accepted rules for reporting RCTs (222) and should adhere to the CONSORT statement (109).

Investigators and sponsors should negotiate timelines for publication at the onset and these should ideally form part of the protocol.

4 Toolbox (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 IHS
1.1.2	Non-target 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

(continued)

Continued

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 dairy	Use a simple report diary
1.3.2	Percentage of patients pain-free within 2 h	Should be primary measure of efficacy, see text
1.3.3	Sustained pain freedom (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 (Special Guidelines (103))
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 freedom 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
2.1.4	Duration of disease	> 1 years
2.1.5	Duration of observation	3 months retrospective and 1 month prospective recording
2.1.6	Age at onset	< 50 years
2.1.7	Age at entry	18–65 years
2.1.8	Gender	Both female and male patients
2.1.9	Concomitant drug use	See text

(continued)

Continued

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 1 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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