


Guidelines of the International Headache Society for controlled trials of preventive treatment of migraine in children and adolescents, 1st edition

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Abstract

Background: Because the results of clinical trials of investigational treatments influence regulatory policy, prescribing patterns, and use in clinical practice, high quality trials are an essential component of the evidence base for migraine. The International Headache Society has published guidelines for clinical trials in adults with migraine since 1991. With multiple issues specific to children and adolescents with migraine, as well as the emergence of novel trial designs and advances in pharmaceuticals, biologics, devices, and behavioural interventions, there is a need for guidance focusing on issues specific to the conduct of clinical trials in children and adolescents with migraine.

Objectives: The objective of these guidelines is to provide a contemporary, standardized, and evidence-based approach to the design, conduct, and reporting of well-controlled clinical trials of preventive treatment of migraine in children and adolescents.

Methods: The development of these guidelines was based on guidelines previously published by the International Headache Society and regulatory bodies. The recommendations are evidence-based, where available. The process included consultations among various committees, roundtable discussions among stakeholders (lay people and the pharmaceutical industry), and open consultation with the IHS membership on the final draft.

Results: A series of recommendations addressing the major issues in clinical trials in children and adolescents with migraine is provided. Recommendations are supported by evidence-based practice and validated methodologies, where available. Supporting comments are provided to clarify ambiguities.

Conclusions: These guidelines should be consulted and used in designing and conducting clinical trials of preventive treatments in children and adolescents with migraine.

Keywords

Migraine, migraine without aura, migraine with aura, chronic migraine, acute treatment, preventive treatment, child, adolescent

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Introduction

The International Headache Society (IHS) has developed and published Guidelines on controlled trials in primary headache disorders since 1991 (1–6). In 2008, the first edition of the guidelines for migraine clinical trials was expanded, and the first edition of the guidelines for controlled trials for preventive treatment in chronic migraine was issued (3). In the 10 years since

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the preventive trial guidelines became available, they have been used in the design and conduct of many clinical trials, testing a wide range of drugs, biologics, and devices. Lessons learned from this body of work were incorporated into a 2018 update (6).

Migraine is common in children and adolescents. The prevalence of migraine in children and adolescents is estimated at 7.7% in a systematic review of population-based studies (7). The prevalence of chronic migraine in adolescents (12–17 years of age) is estimated at 1.7%, with at least half of those with chronic migraine overuse medication (8). Frequent migraine and chronic migraine have been shown to cause significant adverse impact on quality of life of children and adolescents (9). Although the guidelines in adults recognise several issues specific to trials in paediatric subjects (6), there was an unmet need for guidelines devoted to children and adolescents. To meet the need, the IHS has developed these Guidelines. Intended to assist in the design and conduct of well-controlled clinical trials of pharmaceuticals, biologics, devices, and behavioural interventions, with the ultimate goal of reducing the frequency and burden of migraine in children and adolescents, they address general issues associated with migraine clinical trials, as well as those specific to trials with non-adult participants. Readers seeking general advice about clinical trials may wish to consult works on trial methodology and good research practices (10–12), as well as general discussions of these issues (13–15).

These guidelines are an outgrowth of the preventive trial guidelines for adults and, similarly, they are informed by the ethical and professional responsibilities of the IHS. They have been designed to ensure compliance with the rules and requirements of international, national, and local regulatory bodies. These guidelines use consistent terminology and language, and while they are intended to be specific, measurable, achievable, relevant, time-oriented (i.e. SMART) and potentially applicable worldwide, they acknowledge the potential need for local variations. Recommendations are brief and, where available, supported by evidence-based practice and validated methodologies. Comments supporting the recommendations are included to clarify any ambiguities that may arise.

The process of consultation on the contents and the format of the guidelines went through several stages over a 6-month period. The first stage involved consultation among members of the Clinical Trials and the Child and Adolescent Standing Committees. The product of those consultations was subjected to a second stage, in which roundtable discussions among stakeholders (lay people and the pharmaceutical industry) were employed to refine the initial draft. The final, published version of the Guidelines is the result of a third

stage of review, during which the Committees solicited open consultation by IHS members and incorporated many thoughtful revisions throughout.

Participants

Selection

Recommendations. Identification of participants should be based on clearly defined inclusion and exclusion criteria. They should specify the population to be studied and the diagnoses, demographic features, concomitant health conditions, treatments, and populations to exclude.

Comments. Appropriate identification of participants in clinical trials is a critical factor in design and replication; therefore, inclusion and exclusion criteria need to be carefully defined prior to the initiation of the trial. The engagement of the participants as well as their parents/guardians will be necessary to make sure that parental interpretation is consistent with participants' responses.

Diagnosis

Migraine

Recommendations. The most recent version of the International Classification of Headache Disorders (ICHD) should be used for diagnosing migraine types and subtypes in clinical trials.

Comments. The ICHD has been highly successful in diagnosing children and adolescents in clinical trials. The first edition was published in 1988 (16); second and third editions were published in 2004 (17) and 2018 (18), respectively. With the exception of childhood periodic syndromes, notes and comments have been used to distinguish the specific features of paediatric migraine, including shorter duration, frontotemporal location, and allowance for parental observation (16–18). The current edition of the ICHD sub-classifies migraine into subtypes that are not mutually exclusive, including migraine without aura, migraine with aura, chronic migraine, and episodic syndromes associated with migraine (18).

Chronic migraine

Recommendations. Chronic migraine should be considered in the development and proposed analysis of prevention studies in children and adolescents with migraine. The diagnostic criteria for chronic migraine

should comply with those of the latest available version of the ICHD.

Comment. When the frequency of attacks is used to define treatment groups for a clinical trial, additional diagnostic considerations are sometimes needed. For chronic migraine, the diagnosis in children and adolescents is the same as for adults: 15 or more headache days per month with at least 8 days having migraine features for at least 3 months. Trials can be designed to include or exclude subjects with chronic migraine explicitly or to include all subtypes of migraine and pre-plan a sub-analysis of migraine outcomes based on number of headache days per month. Investigators should note that because there are no reliable data on the prevalence of chronic migraine in children under 12 years of age, it may be difficult to recruit qualified subjects for clinical trials. It is therefore recommended that close monitoring of enrolment rates and an interim analysis be included in the trial design. It should also be noted that while “episodic migraine” is a term commonly used to describe migraine occurring on fewer than 15 days per month, ICHD simply refers to it as “migraine” in contrast to chronic migraine.

Medication-overuse headache

Recommendations. Children and adolescents with medication overuse can be included in clinical trials, provided that the pattern of overuse remains stable through all phases of the trial (i.e. screening, baseline, and treatment), unless it is required by the nature of the trial (e.g. an investigation of withdrawal regimens).

Comments. Many adolescents with chronic migraine may overuse acute medications (8,19) and meet ICHD-3 criteria for medication-overuse headache: Headache occurring on 15 or more days per month in individuals with a pre-existing primary headache and who have been overusing, for at least 3 months, simple analgesics (paracetamol or ibuprofen) on 15 or more days per month or triptans, opioids, or combination analgesics on 10 or more days per month (18). Since discontinuation of overused drugs can confound outcomes and is associated with variable headache improvement, it is acceptable to include participants who are overusing acute medication, as long as a stratified randomization procedure is used to ensure that treatment groups will be balanced for medication overuse. Depending on trial objectives, participants may be selected or stratified based on the type of acute medication overused (refer to Section 2.5 for information about stratification).

Participants overusing barbiturate-containing analgesics and opioids and participants with medical conditions attributable to medication overuse (e.g. peptic

ulcer disease from overuse of NSAIDs) should have adequate and careful discontinuation prior to enrollment (20) with complete cessation over 4–8 weeks. These patients should not be included in conventional clinical trials but can be included in specifically-designed studies targeting these patients.

During all research trials, the use of all medications for the treatment of headache episodes should be accurately recorded by child and/or guardian, as appropriate. The use of acute medications during the treatment phases needs to be captured and evaluated as a secondary or tertiary treatment outcome.

Other headaches

Recommendations. Subjects experiencing attacks of probable migraine – attacks missing one of the features required to fulfil all criteria for a type or subtype of migraine – are permitted in trials of chronic migraine as part of the ≥ 15 days/month (18) as long as the participant meets the ICHD criteria for chronic migraine.

Comments. Children and adolescents with other types of primary episodic headaches (e.g. tension-type headache, trigeminal autonomic cephalalgias) should be permitted to enrol in clinical trials of preventive migraine treatment, provided that their attacks occur on no more than 1 day per month and can be clearly distinguished from migraine. Individuals with any secondary headache condition (except medication-overuse headache) should be excluded.

History of migraine

Recommendation. Migraine should be present for at least 6 months prior to trial inclusion.

Comments. Migraine is a primary headache disorder that may first occur in children or adolescents as a variant rather than the characteristic phenotype. Therefore, participants should have a history of at least 6 months of recurrent headache to ensure its primary nature and to account for atypical presentations and spontaneous fluctuations in migraine frequency. The history can be verified through a combination of medical record documentation and recall by participants and/or parents or guardians.

Age at onset

Recommendations. The age of migraine onset should be accurately recorded to assure stable history of a primary headache disorder.

Comments. Migraine may start in early childhood but not be clearly recognised by parents or guardians. The initial presentation may be a migraine variant, and it may not develop into the typical phenotype until a child reaches 6 years of age. This may make enrolment of young children challenging. As medications for the prevention of migraine may be used in school-aged children, these age groups must be considered when designing studies.

Age at entry

Recommendation. Trials should be designed to assure adequate age strata for inclusion of children and adolescents who are likely to be exposed to the medication or treatment being tested.

Comments. In clinical trials, children should be defined as participants aged 6 to 11 years, inclusive, and adolescents should be defined as participants aged 12 to 17 years, inclusive. Regulatory agencies may require separate trials in children and adolescents. Some development programmes may include participants who are younger than 6 years old, but findings in these subjects should be considered observational and safety testing.

Enrolment

Recommendations. Participants enrolled into clinical trials should meet all predefined protocol inclusion criteria and not meet any of the predefined exclusion criteria, and eligibility should be documented at baseline and confirmed at randomization. Information about the trial and preventive treatment, especially with respect to safety in children and adolescents, should be carefully assessed before distribution to participants and parents or guardians. Enrolment should be limited to one clinical trial at a time, with extensions (e.g. to assess long-term safety) considered part of the same trial.

Comments. According to the *Guideline for Good Clinical Practice* (21), participants and their parents/guardians should be given a clear explanation of the purpose of the trial, their role in its conduct, the obligations with which they are expected to comply, and the risks they assume by agreeing to enrol. This information should be presented in a way that does not exaggerate placebo and nocebo responses. Other important trial-related information should include instruction on the importance of compliance and adherence, as compliance with migraine preventive treatments is often poor (22–23), resulting in decreased efficacy. Group characteristics regarding inclusion criteria should be reported (e.g. mean age, BMI, age of migraine onset, age of chronic

migraine onset, headache days, migraine days, concomitant preventive medications, days of intake of acute medications, type and number of acute medications, presence of aura). Enrolment in more than one trial is discouraged because subjects who participate in multiple clinical trials may influence the generalizability of results; caution should be taken during recruitment and screening. Participation in prospective registries without treatment regimens (i.e. non-interventional) is possible.

Sex

Recommendations. Females who are pregnant, may become pregnant, or breastfeeding should be excluded from participation in a clinical trial if the investigational treatment has a potential for toxicity to the foetus or infant or when the potential for toxicity is unknown.

Comments. Adolescent females should adhere to strict and effective contraceptive measures in the run in and during the whole trial period. Should a participant become pregnant during the trial, her participation in the trial should be immediately terminated and a predetermined procedure should be followed.

Coexistent disorders

Recommendation. Participants must be screened for all coexistent (including psychiatric) conditions to exclude those that may have an impact on the conduct or results of the trial.

Comments. Depending on the nature of the trial, some coexistent disorders may be a reason for exclusion because of the potential for exacerbation of an underlying condition, or because the concomitant management of coexisting conditions may confound study results or make adherence and compliance with medications or trial obligations difficult (24). Since depression, anxiety, obesity, and chronic pain are common in patients with migraine (25–27), their presence, classification, and associated treatment needs must be assessed prior to inclusion in a clinical trial. Participants with coexisting conditions may be included if they are prospectively defined and stable on a treatment regimen that does not interfere with the interpretation of trial results. However, participants should be excluded if they have severe depression, suicidal ideation, or when treatment of these conditions may interfere with trial treatments or the condition under evaluation. Participants should be excluded if they have a substance-use disorder, according to the criteria in the *Diagnostic and Statistical Manual of Mental Disorders*

— *DSM 5* (28) or are overusing alcohol or other illicit drugs. Participants who are allergic or have shown hypersensitivity to compounds similar to the trial drug should also be excluded.

Treatment history

Recommendations. Participants who have failed previous preventive treatments can be included in clinical trials. Treatment failure is defined as insufficient efficacy following adequate doses and adequate duration of treatment (according to participants, guardians, and/or their physicians) or intolerable side effects and/or safety concerns.

Comment. A history of response to previous treatment(s) for headache, as well as the possible reasons for failure, should be recorded at the point of inclusion. Insufficient efficacy and inadequate response can be ascertained from subject self-report and/or communication with the treating healthcare professional.

Trial design

When designing a trial, it is essential to consider its burden on participants, their families, and the investigators and staff. Trials with an excessive burden may restrict or inhibit enrolment, and they increase the risk of failure due to administrative rather than medical issues.

Blinding

Recommendations. Clinical trials must use double-blind designs to establish the efficacy, safety, and tolerability of preventive treatments, as well as to remove investigator and participant bias.

Comments. Unblinding due to adverse events (AEs) can be a significant factor in clinical trials of preventive migraine treatments. To evaluate the quality of blinding after the trial, participants and investigators can be questioned regarding their opinion/best guess about which treatment group they were assigned to during the trial.

Controls

Recommendations. Treatments used for the prevention of migraine should be compared with placebo, sham, attention control, or an active comparator. When two presumably active treatments are compared, a placebo control can provide for a measure of additional assay sensitivity, if appropriate.

Comments. As most migraine trials in paediatric populations evaluate agents that have already demonstrated efficacy and safety in adults, children and adolescents may enter clinical trials with an increased expectation of a positive response. This expectation, combined with a desire to please investigators among participants and guardians, may contribute to the increased placebo response observed in studies of youth. To control for this effect, clinical trials should be blinded and compare treatments under evaluation with placebo or an active comparator that has demonstrated superiority to placebo. Investigators should note that in trials with active comparators, findings of equivalent efficacy do not establish the efficacy of either treatment, but they may be used to demonstrate non-inferiority; efficacy can only be hypothesized if previous research has shown the control to be superior to placebo.

Design type

Recommendation. In trials of preventive treatment, parallel-group designs are recommended over crossover designs.

Comments. Parallel group trials are the preferred trial design. In crossover trials, each participant is offered at least two treatments in a random order with a wash-out period in between, allowing each participant to act as his/her own control as well as allowing a group comparison.

Crossover designs have significant disadvantages in trials of preventive treatment, including the possibility of a carryover effect, which cannot be controlled with certainty even with washout periods, and the need for a longer study duration, which increases the likelihood of participants dropping out of the trial. Crossover designs may have a place in trials on acute treatment of migraine. Additionally, novel design methods may be considered, including placebo or active agent run-ins, identification of non-responders to standard treatments, add-on treatments, and new approaches such as Sequential Multiple Assignment Randomized Trial or Multiphase Optimization Strategy (29).

Randomization

Recommendation. Participants in trials of preventive migraine treatment should be randomized using an established method that has been specified prior to trial initiation and not altered once the trial has begun.

Comments. Randomization should occur after the baseline period, and randomized participants become part of the intention-to-treat population, whether they complete the trial or not. If they do not complete the trial,

their randomized position should not be reassigned. Because recruitment for preventive migraine trials tends to occur over extended periods, participants should be randomized in relatively small blocks (e.g. 4–8 or 4–10) or important strata intermittently reviewed (e.g. 2.5) to ensure balanced randomization across treatment groups.

Stratification

Recommendations. Stratified designs are recommended in parallel-group trials to overcome important confounding factors, such as age, sex, comorbidity, and use of concomitant medications.

Comments. Randomization alone does not ensure that treatment groups will be balanced for factors that can influence treatment response, and imbalanced treatment groups can lead to spurious results, particularly when sample sizes are modest.

Two common approaches address the problem. The more widely used approach, which simplifies trial logistics, is to include potential confounders in planned statistical analyses. Another method, stratified randomization, ensures that groups are balanced by using the confounder to assign subjects to treatment groups; it should be considered for known confounders that can be readily measured at baseline, including the number of prior preventive medications and acute medication overuse. It is difficult to do stratified randomization for multiple factors, and stratified randomization complicates trial logistics. For this reason, stratification needs to be limited to a certain number of factors and dependent on sample size (refer to Section 4 for more information about statistics).

Data collection

Recommendations. It is essential to collect data about headache characteristics, use of medications, AEs, and compliance. Well-designed paper or electronic data collection systems should be used.

Comment. Paper and electronic data collection systems have inherent advantages and disadvantages. Electronic systems reduce recall bias and have the advantage of time stamps, remote monitoring, and alerts. However, they are at risk of device failure, digital backup loss, and programming errors, and they lack a hard copy backup. Paper-based systems maintain a hard copy backup, but they lack time stamp and remote monitoring capabilities. To ensure participant comprehension and the collection of all protocol-required data, the collection system should be chosen and validated prior to initiation of the trial.

Whichever type of system is chosen, its design should incorporate several elements. Case report forms should be validated and easy to use; the US National Institutes of Health has developed migraine-specific common data elements that can be used to guide their development (30). Adverse event reporting should be standardized, and data should be collected during all site visits; serious AEs need to be reportable within 24 hours of their occurrence. The participant interface should maximise ease of use and comprehension and minimise the response burden associated with entering data. Question sets should be written to ensure that the time participants take to complete them is similar whether or not they have an attack. Trial diaries should also be standardised across sites and, if necessary, translated to account for language and cultural differences. They should be designed with the expectation that parents or guardians are likely to assist or take responsibility for keeping diaries for children (i.e. < 12 years), while adolescents will complete trial diaries themselves, using parents or guardians for assistance only if needed.

Baseline period

Recommendations. A minimum 28-day prospective baseline period (up to 56 days) is recommended using a headache diary that captures the diagnostic criteria for migraine and other important information, including attack frequency, duration, headache characteristics, and associated symptoms.

Comments. The baseline period is used to confirm that enrolled subjects are eligible for trial and can adhere to trial data collection procedures, as well as to provide baseline data for the primary outcome measures (13,18,31,32). Information collected about attacks occurring during the baseline period should include headache duration; headache intensity; the presence of associated symptoms (nausea, photophobia, phonophobia); the presence of aura; impact on the ability to function; the use of acute treatment (type and frequency); and response to acute treatment. For children and adolescents, a 28-day baseline period is usually adequate for verifying the stability of headache frequency (33). However, because attack frequency may vary from week to week and month to month, a baseline period of 56 days may be necessary if headache frequency appears to be unstable. Investigators considering baseline periods longer than 28 days should be aware that they can make enrolment more difficult, increase pre-randomization dropout rates, and delay treatment for patients with unmet treatment needs. Inclusion and exclusion criteria need to be carefully considered before the baseline period to minimise variability in the trial population, as high variability in

baseline frequency diminishes statistical power for primary efficacy measures.

Duration of treatment

Recommendations. A minimum treatment period of 84 days (12 weeks) is recommended. Treatment periods longer than 84 days can be used to evaluate cumulative benefit or persistence of efficacy and collect additional safety and tolerability data.

Comments. The duration of treatment needed to determine the efficacy or failure of an investigational therapy for prevention of migraine is not well established. Treatment periods exceeding 12 weeks may increase the likelihood of identifying a significant separation between active treatment and control, and they may help identify additional AEs or data about time to relapse. However, participants in longer trials must remain on placebo for an extended period, increasing the chance of withdrawal due to lack of efficacy, and an extended wait for positive results may make them less clinically meaningful. With treatments awaiting approval, long-term trials maintain access to care among subjects who participated in the placebo arm of a controlled trial and provide useful information (e.g. safety, adherence to treatment). Shorter treatment periods (e.g. 8 weeks) may be appropriate for treatments with pharmacokinetics suggesting a rapid onset of action that do not require dose titration/escalation. Alternatives to duration of treatment can include trajectory of response or time to a pre-specified response (i.e. survival curves).

Follow-up

Recommendations. After the randomized treatment period, participants should be followed prospectively for the evaluation of safety and potential rebound phenomena. Ideally, participants should continue to complete a daily diary and record any perceived AEs during this follow-up period.

Comments. Randomized withdrawal trials – in which the entire cohort is initially treated with active treatment and then randomized after 12 weeks in blinded fashion to continuation of active treatment or placebo – may be considered. This design can help to identify rebound phenomena after treatment termination and detect possible long-term modification of migraine risk beyond the actual treatment period.

Dosage or procedures

Recommendations. In phase II trials in paediatric populations, investigators should use the results of trials in

adults and the known pharmacokinetics and pharmacodynamics (e.g. minimal effective dose and maximum tolerated dose) as a guide in testing the widest possible range of doses of a preventive treatment. In phase III trials, one or two doses can be administered to participants who have been stratified by weight to account for size, age, and possible impact on volume of distribution. Dosing in trials of devices and non-pharmaceutical products should be adjusted to match participants' stage of development.

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

Concomitant treatment

Recommendations. The use of all treatments for headache should be accurately recorded in trial diaries by participants and/or guardians. Acute medication use (type and frequency), during the treatment phases should be captured and evaluated as a secondary or tertiary treatment outcome. Therapies with potential migraine preventive capability (e.g. vitamin supplements, complementary treatments, bio-behavioural therapy, neurostimulation, occipital nerve blocks, onabotulinumtoxin-A) should be disallowed unless the dosage has been stable for at least 2 months before randomization and will not be changed during the trial (34,35).

Comments. The trial protocol should pre-specify concomitant medications that are permitted for use upon enrolment and/or during the trial. It should also establish clear guidelines for the optimal use of acute treatments, addressing allowable changes in acute treatment type, dosage, formulation, or mode of administration, as well as medication overuse. Participants should be given clear instruction on the use of acute therapies so that any increases or decreases can be factored into analyses of trial data. If concomitant treatments are allowed during a clinical trial, care should be taken to assure that use is balanced across the arms of the trial. Investigators should ensure that usage instructions are standardised across treatment centres.

Monitoring

Recommendations. Participants in clinical trials should be monitored regularly. Typically, they are seen at screening, at the beginning and end of the baseline period, and after randomization/initiation of treatment. Subsequent visits are contingent upon the treatment being tested and the duration of the trial. Face-to-face visits are recommended every 4 to 8 weeks. Telephone or

video contacts may suffice between visits, and remote monitoring methods should be encouraged to aid adherence. Monitoring of adherence, via pill counts, device reminders and smart packaging should be considered.

Comments. Regular participant contacts are important to determine eligibility, ensure compliance, and monitor for AEs.

Outcome measures and endpoints

Recommendations

All primary and secondary endpoints, treatment groups (e.g. active treatment or placebo), comparisons (active vs. placebo or baseline), and treatment periods (e.g. 28 days [4-week] or 84 days [12-week]) should be prospectively defined and depend on the trial objective. Calculations to ensure trials are adequately powered to detect differences between treatments for the primary endpoint should be included in the trial protocol.

Comments

Trials with multiple primary endpoints or three or more treatment groups may encounter multiplicity issues. In trials with multiple primary endpoints, investigators may manage them by proposing a composite endpoint or using hierarchical testing procedures. If investigators decide to use a multiple comparison adjustment, it needs to be defined prior to trial initiation and reflected in sample size and power calculations. *Post hoc* unplanned analyses should be avoided; if employed, results should be considered exploratory.

Primary endpoints

Recommendations. There are two possible primary efficacy endpoints in clinical trials of preventive treatment: Change in headache frequency, as measured by headache days or migraine days, and 50% responder rate as measured by migraine days. Whichever of these two endpoints is not selected as the primary endpoint should be included as a secondary endpoint.

Comments. A headache day is defined as any perception of headache during a 24-hour period starting and ending at midnight. The definition may be limited to headaches of moderate or severe intensity, and the minimum 2-hour duration variable is optional, as acute treatment use may reduce headache duration. A migraine day is defined as a 24-hour period starting and ending at midnight during which a headache with features matching ICHD criteria for migraine is perceived; if participants use and respond to acute

treatment, attacks they believe would have met the ICHD definition of migraine can be included.

The use of headache days allows the use of a relatively simple trial diary. Participants indicate whether a headache was present (yes/no); its baseline and peak intensity (none, mild, moderate, or severe); its duration (more or less than 2 hours); acute treatment type (triptan or other); and, as an option, response to treatment. Using migraine days requires a more detailed diary to capture all migraine-related features and enable classification. In addition, defining frequency as migraine days can be problematic if the participant is allowed to treat acute attacks, as not all features may develop prior to response. Because the change is calculated by subtracting headaches per unit time on treatment from headaches per unit time at baseline, the accuracy of the baseline assessments directly influences trial results. As trial diaries become more complicated, a pre-specified strategy for handling missing data should be established.

The responder rate can be defined as an absolute reduction in headache frequency, a reduction relative to a predetermined threshold (i.e. one headache/week), or a percentage change relative to baseline frequency. Responder rates based on percentage change have traditionally been set at 50% or greater, but other rates (e.g. 30%, 75% and 100%) may also be considered. Specific responder rates used in clinical trials must be defined *a priori*. Responder rates can be used in meta-analyses, but population definitions of response should not be used to determine clinically meaningful treatment effects in individuals.

The time periods for analyses of efficacy should be equivalent. Thus, if a baseline period is 28 days, the final 28 days of the treatment period should be assessed. As a secondary endpoint, each 28-day interval can also be compared with baseline to demonstrate the trajectory of response.

Secondary endpoints

The secondary endpoints listed below are not presented in order of priority and are subdivided based on the components they explore. Unless chosen as the primary outcome, any of the outcomes in Section 3.1 should be considered as a secondary outcome.

Headache-related characteristics

Maximum headache intensity. Maximum headache intensity is not recommended as a primary outcome measure, but it is important to record decreases in intensity because they indicate reductions in disability. Participants should be instructed to record headache intensity on a 4-point scale, where 0 = none, 1 = mild,

2 = moderate, and 3 = severe, and these values can be used as proxies for disability; that is, respectively, absent, mild (does not interfere with activities), moderate (interferes with some but not all activities), or severe (stops all activities). Alternatively, a 100-mm Visual Analogue Scale (VAS), an 11-point numerical rating scale (NRS), or a Faces scale (36) (or equivalent) can be used. The NRS may offer a higher discriminatory capability than a categorical scale for showing differences in pain intensity (37).

Features and characteristics. Individual migraine-specific features and characteristics should be collected in diaries. Therapies studied may have a differential change in characteristics and help with identification of patients that are more appropriate for a particular treatment.

Headache hours per 28 days. This outcome can be calculated using the start and end time of headaches. In making this assessment, it should be noted that if participants go to sleep and awaken with headache, sleeping time should be counted as headache hours. If they go to sleep with headache and awaken headache free, the headache hours calculation should still include sleeping time, as it cannot be determined when headache resolves during sleep.

Other. Other secondary outcomes, such as frequency of migraine aura, may be considered, but they need to be defined prior to trial initiation.

Depression and anxiety. Depression and anxiety levels should be recorded at the time of randomization and at the end of the treatment period. Validated scales for depression in adults include the Patient Health Questionnaire-9 (PHQ-9) (38), Patient Health Questionnaire-4 (PHQ-4) (39), Beck Depression Inventory (BDI) (40), and the Hospital Anxiety and Depression Scale (HADS) (41). For assessments of anxiety, besides HADS, the State-Trait Anxiety Inventory (STAI) (42) and the Generalized Anxiety Disorder questionnaire (GAD-7) (43) can be used. Specific and validated adolescent versions of these tools (i.e. PHQ-A (44), BDI-II (45), HADS (46), STAI-Y (47), GAD-7 (48)) should be used where possible.

Disability assessment

Recommendation. The Pediatric Migraine Disability Assessment (PedMIDAS) can be used to assess the effect of treatment on participants' disability and functioning (49).

Comments. The PedMIDAS is a validated tool designed to depict migraine-related disability in school-aged children and adolescents. This six-item, self-administered questionnaire addresses the subjective impact of migraine on school, home, and social functioning over the previous 3 months (49). An evaluation period of at least 3 months is essential, as the nature of attacks can vary from week to week in young subjects, and a shorter time period may not characterize the totality of migraine's influence on a young person's life. Other patient-reported outcome instruments may be used as they are validated.

Exploratory outcome measures

Recommendation. Several measures can be used to capture exploratory outcomes that may be clinically meaningful and correlate with primary or secondary endpoints, including the number of headache-free days, number of symptom-free days, and biomarkers.

Comments. Taken together with results on primary and secondary outcome measures, exploratory outcomes such as headache-free days, symptom-free days, and biomarkers can provide valuable insights into the efficacy of a preventive treatment. Headache-free days are defined as days with no headache, associated symptoms, including physical function, cognitive or emotional impairment that is directly attributable to migraine. Symptom-free days are defined as days free from prodromal, headache, and postdromal symptoms; they are best quantified through the headache diary. As migraine has a strong genetic component, assessment of biomarkers should be considered. These can include DNA polymorphisms or structural changes, RNA expression profiles, pharmacogenomics response patterns, neuroimaging, and neurophysiology response changes.

Pharmacoeconomic endpoints

Recommendations. Assessments of the economic value of preventive treatment for migraine should capture direct costs (price of medical treatment) and indirect costs (lost time from school or work).

Comments. The economic burden of migraine to individuals and society may be offset or reduced by effective preventive treatment, and rigorous demonstrations of cost-effectiveness can encourage the development and implementation of health policies prioritizing migraine. The direct costs of medical treatment (i.e. purchase price) can be calculated using diaries or time-stamped electronic data. Indirect costs (i.e. due to absenteeism and/or impaired performance at work, school, home, and social activities) can be estimated using self-report

diaries, experience-based sampling, employer and school work records, or with PedMIDAS. In trials involving children and adolescents, migraine-associated decrements in the productivity and activity of parents and guardians represent an important component of indirect costs. The mean change from baseline can be measured by the Work Productivity and Activity Impairment Questionnaire (50) for parents and guardians; a migraine-specific version is available at the developer's website (51).

Adverse events

Recommendations. Documentation of AEs and serious AEs that occur during a clinical trial should follow the nomenclature and hierarchy of the Medical Dictionary for Regulatory Activities (52).

Comments. Adverse events are not necessarily related to the treatment(s) under assessment in a clinical trial. To detect any unexpected and unwanted effects, subjects in clinical trials should record AEs openly, and investigators should determine whether any AEs reported during a trial are related to treatment. The standard methodology for collecting safety and tolerability data includes spontaneous reports recordings, open-ended questions, and direct questioning. Results should be reported separately for active and placebo treatment. Detailed reporting of AEs should follow the guidelines of local Institutional Review Boards, regulatory authorities, and the *Guideline for Good Clinical Practice* (21). It should be noted that regulatory authorities require more detailed reporting of AEs with new experimental treatments (53,54). In preventive regimens prescribed in clinical practice, AEs often occur before maximum efficacy is reached. They are an important problem that frequently leads to discontinuation of treatment. Therefore, the incidence of AEs in clinical trials – especially those leading to discontinuation – should be regarded as one of the major measures of the tolerability of a preventive migraine treatment.

Statistics

Recommendations

Pre-plan the analysis of data and define the following issues as *a priori*:

- Primary measurement time to determine study outcome
- Statistical analysis plan
- Primary efficacy endpoint
- Modalities of data collection to evaluate change in efficacy variables
- Sample size needed to achieve appropriate power to detect differences between treatment groups
- Comparisons between the treatment phase and baseline phase as a primary endpoint, secondary endpoints, or both
- Rules for the imputation of missing data for designated variables
- Method for comparisons between treatment groups

In addition to these issues, it is also important to prospectively define the analysis population.

Comments

Statistical analysis is based on certain assumptions. The statistical plan needs to include the methods and tests that will be used to test these assumptions. Also, investigators need to propose alternative analysis plans in the event that any assumptions are not met. For example, if a normal distribution assumption is not met by the data collected during the trial, analysis can be using a Wilcoxon rank sum test instead of a two-sample t-test. Normality assumptions can be checked using various tests or graphical methods readily available in statistical software. If imbalances in treatment groups are observed for key variables of interest, regression methods must be used to account for them. The effect size for the primary outcome measure(s) should be calculated with available statistical methods, which will enhance estimates of efficacy and facilitate comparisons with results from other trials (55–56).

Participants should be analysed according to the randomization assignment, regardless of actual treatment received (intent-to-treat population, analysed as randomized). For safety variables, it might be reasonable to analyse participants according to the treatment the participant actually received (safety population, analysed as treated). To have data for all participants in the intent-to-treat population, consider imputing missing data for at least the primary variable of interest as either a primary or a sensitivity analysis. Alternate statistical analysis may be used if verified by a statistician. For example, if the headache stop time is to be captured and is unknown, a decision rule might be to assume that the headache stopped at the end of the last day (e.g. 23 h 59 sec) that it was reported to be ongoing.

When determining the outcomes and statistical power of a trial, clinically meaningful differences need to be considered to establish the effect size and Minimal Important Difference. These values should be based on expert opinion, paediatric healthcare providers, and participant preference obtained through a review of existing trials in adults and, if possible, surveys. The determination of a clinically meaningful effect assures that sample sizes in clinical trials will be adequately powered to show

a clinically relevant benefit over placebo, as underpowered trials are not adequate for proving the efficacy but may be hypothesis generating and provide information on tolerability. This may require large samples and, to achieve appropriate sample size, multi-centred trials, which have the advantages of avoiding the introduction of selection bias from a single site and of offering access to an appropriate number and diversity of participants.

In reporting trial results, summary tables for each treatment and for each measurement time should include the number of participants and descriptive statistics (mean, standard deviation, median, minimum, and maximum) and/or response frequencies.

Trial registration

Prior to the initiation of a trial, it should be pre-registered in a register acknowledged by regulatory authorities, such as clinicaltrials.gov, clinicaltrialsregister.eu, or a similar regional or national official database.

Publication of results

Publication of trial results is necessary and should include all primary and secondary efficacy endpoints and all safety data, whether positive or negative. Before any trial-related activities are initiated, a Steering Committee (refer to Section 2.9 for details) should agree on timelines for publication and, if possible, include them in the protocol; a Publication Committee may also be formed. At the initiation of the trial or at the end of recruitment, a design paper with baseline data may be published. Authorship of trial-related publications should be based on the criteria of the International Committee of Medical Journal Editors (57).

Ethics

All clinical trials must follow standardised ethical and safety guidelines, and they must be approved through appropriate Institutional Review Boards or Ethics Committees. In trials involving children and adolescents, participants must provide informed assent, and parents or guardians must provide informed consent. Trials must be conducted in accordance with the Declaration of Helsinki (58) and *Guideline for Good Clinical Practice* (22), and they must follow the rules of local regulatory authorities, such as the European Commission on Better Medicine for Children (59).

Conflicts of interest

To maintain the credibility of a trial, authors must declare their conflicts of interest. A conflict of interest exists whenever professional judgment concerning a

primary interest (e.g. subject wellbeing or the validity of research) may be influenced by a secondary interest (e.g. financial relationship to a trial sponsor). Financial relationships that represent potential conflicts of interest include employment, consultancies, research grants, fees and honoraria, patents, royalties, stock or share ownership, and paid expert testimony. Investigators should avoid agreements with sponsors, both for-profit and non-profit, that restrict access to trial data, limit its analysis and interpretation, or interfere with the independent preparation and publication of manuscripts. Note that conflicts of interest extend to an investigator's immediate family (partner and children).

Independent data safety monitoring board

An independent data safety monitoring board and predefined stopping rules for futility or safety are recommended for phase III trials. Independent interim analysis by the data safety monitoring board should be considered for assessment of the pre-defined stopping rules.

Steering committee

For phase III trials sponsored by industry, the formation of a Steering Committee comprised of academics, statisticians, and (if appropriate) company representatives is recommended. For investigator-initiated trials (i.e. developed and sponsored by independent investigators or academia), a Steering Committee is not necessary. Whether or not a committee is formed, investigators and sponsors are responsible for all aspects of a clinical trial, including conception; design; operational execution; data handling; data analysis and interpretation; subsequent reporting and publication; and compliance with all local laws and regulations.

Post-approval registries

The IHS recommends post-approval product registries (i.e. prospective open-label observational studies) to evaluate the use of newly approved acute treatments in clinical practice. Registries generate real-world data on long-term efficacy, tolerability, and safety. They also measure compliance and adherence. Registries for acute migraine treatments may also include individuals with relevant coexistent and comorbid diseases (e.g. chronic pain syndromes, cardiovascular disease) who were excluded from clinical trials for acute migraine.

Health Technology Assessment

In some countries, Health Technology Assessment bodies require dedicated evaluations of cost-effectiveness

and calculations of the cost-benefit ratio as a pre-condition of reimbursement. Data collected for these assessments include office visits, emergency room use, diagnostic tests, hospital admission, and

the cost of treatment; days lost from work or school (or their equivalents) may also be assessed. A comparison with an approved treatment may be required.

Clinical implications

- These guidelines will help to standardise the design and conduct of clinical trials of preventive treatment in children and adolescents with migraine.
- They have the potential to influence multiple factors in the preventive treatment of paediatric patients with migraine.


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