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Inclusion and Exclusion Criteria for Epilepsy Clinical Trials – Recommendations from April 30, 2011 NINDS Workshop

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Abstract

On April 30th, 2011 the National Institute of Neurological Disorders and Stroke (NINDS) held a workshop to identify key problems in recent epilepsy clinical trials and propose approaches to address the barriers that impede development of new therapeutic options for epilepsy. Preliminary recommendations were made for selection criteria for subjects entered into epilepsy trials that maximize the scientific impact of the trial and increase the ability to recruit appropriate subjects efficiently and safely. These recommendations were further refined by the authors following the workshop, and subsequently shared with all NINDS workshop participants and with the participants of the 2011 AED XI workshop on epilepsy trials (approximately 200 participants) for further comment. The working group agreed to a final set of criteria that include updated considerations of subject age, clinical semiology, EEG and imaging results, use of prior and current therapies, co-occurring conditions, and suicidality, among others.

Keywords

Participant selection criteria; clinical trial methodology; recruitment; comorbidity

Introduction

Over the last two decades, ten new antiepileptic drugs (AEDs) have been brought to market, ushering in the so-called “second and third generation” of antiepileptic treatment. Despite the introduction of these agents, the incidence of drug resistant epilepsy (particularly those types characterized by focal onset seizures) has not appreciably declined, and nearly one third of subjects will suffer from a treatment resistant form of the disorder (Brodie et al., 2012). A “new” generation of AEDs is needed. These should have evidence of efficacy as well as tolerability and favorable pharmacokinetic profiles, necessitating the completion of successful clinical trials for novel antiseizure agents. Such trials must be designed with a conscious effort to balance competing pressures of generalizability, feasibility, and ability to accurately detect meaningful differences in efficacy and safety.

Along with other elements of protocol design, selection criteria (inclusion and exclusion criteria) for clinical trials have become complex. Although this is true for drug trials generally, it is particularly true for epilepsy trials due to the etiologic heterogeneity of the epilepsies and the variety of potential outcomes of the disorder. In addition to these factors, variability may also result from inclusion of patients with epilepsy syndromes other than the ones of interest, both non-epileptic and epileptic events; or events that are uncountable (e.g. flurries), too variable or too infrequent in occurrence. Each of these would make it difficult to establish the efficacy of a new drug. Most newer AED studies have been designed as add-on, in which a new agent is added to the subject’s existing AED regimen. Therefore, there must be requirements for stability of background AEDs. In addition, in order to determine the true adverse event profile of an agent, sponsors aim to restrict enrollment of subjects

exposed to AEDs with serious adverse effects (typically, felbamate and vigabatrin). In current epilepsy trials, potential subjects with other stable chronic, commonly occurring conditions, such as diabetes, heart disease or psychiatric diagnoses, are not consistently included, making results less generalizable to the larger population of patients with epilepsy. Finally, given that many AEDs have been demonstrated to carry some teratogenic risk, women with childbearing potential may be excluded.

For these reasons and others, the entry criteria have made it increasingly difficult to recruit subjects for these trials. Moreover, variability in inclusion and exclusion criteria makes it more difficult to compare outcomes across trials. The NINDS has prioritized clinical trial consistency in order to better compare and aggregate data across epilepsy trials, and to this end has published a set of common data elements to be used in epilepsy clinical studies (Loring, 2011.)

On April 30th, 2011 the NINDS held a workshop attended by clinician scientists engaged in clinical trials research, government agency representatives with an interest in therapeutic trials (NINDS, FDA) and representatives from the pharmaceutical industry that sponsor trials, to discuss strategies to enhance anticonvulsant drug trial recruitment. The emphasis of this meeting was to design a set of rational selection criteria that would be practical and acceptable to all parties and: 1) allow fair access to as many appropriate subjects as possible, 2) allow the trial to proceed safely, 3) fairly balance generalizability and efficiency, 4) maximize the potential to accurately determine an intervention's efficacy and/or effectiveness, and 5) improve consistency across trials.

Session I of the workshop focused on Inclusion and Exclusion Criteria. The charge to the Working Group¹ was to recommend selection criteria for subjects entered into AED trials that maximize the ability to recruit subjects into the study population without enrolling subjects who would either confound results or be at high risk for elevated toxicity, noncompliance, or loss to follow-up. Although there are many different types of epilepsy, the working group specifically dealt with two epilepsy scenarios that have most commonly been included in regulatory trials; focal seizures in the setting of a presumed structural abnormality (previously known as partial seizures), and idiopathic generalized epilepsy. Recognizing that they are equally important, the working group nonetheless left inclusion and exclusion criteria recommendations for Lennox-Gastaut Syndrome and other syndromes and seizure types to be addressed separately because of their complexity. After the workshop, the working group reviewed commonly used inclusion and exclusion criteria in recent trials. Relevant literature was sought to support or refute the criteria. An attempt was then made to arrive at a consensus decision on whether to 1) accept a commonly used criterion, 2) revise a commonly used criterion, or 3) eliminate a commonly used criterion. Once the working group had decided on the specific inclusion and exclusion criteria suggestions, they were sent to the entire group attending the NINDS workshop for comment. Subsequently, they were also sent to all attendees of the AED XI workshop on epilepsy

¹Inclusion and Exclusion Criteria Working Group: Gregory Bergey (Chair), Mary Ann Brodie, Evan Fertig, Jacqueline French, Brandy Fureman, Dale Hesdorffer, Deborah Hirtz, Eric Kossoff, W Curt LaFrance Jr, Mark Versavel

trials (approximately 200 participants) that was held just prior to the meeting for further comment. A final set of criteria was agreed to by the working group and is delineated below.

The selection criteria suggested below are intended to serve as guidelines to facilitate appropriate subject selection. Workshop participants emphasized that the suggested criteria are not requirements for all clinical trials. The Discussion section below describes the rationale for these recommendations. Ideally, these criteria are to be considered the “default” for all trials involving subjects with these specific types of epilepsy. If changes to these parameters are made, the investigator should provide a scientific or medical rationale (e.g. different age ranges for studies in young children, drug carries unique risk for certain subjects, etc.)

In addition, the guidelines suggested here are intended to be iterative. As new information or consensus emerges on these considerations for clinical trials, or on currently controversial topics, the working group anticipates that updated guidelines will be developed and disseminated to the community. For example, the current guidelines were developed during a time of transition from one epilepsy classification system to another (Berg et al., 2010). Because the new classification system does not have a category that specifically identifies each of the populations that have traditionally been enrolled in trials, we use a category name (such as “primary generalized epilepsy”) but describe the population in terms of the new classification methodology.

The recommendations were developed for the two most common patient populations in epilepsy drug trials; subjects with drug resistant epilepsy, with either focal or primary generalized epilepsy. The selection criteria below are presented in a hierarchy as 1) criteria that are relevant to all trials in these populations, 2) criteria that are specific for drug resistant populations, and 3) criteria that are specific for participants with a) focal or b) primary generalized (now called genetic generalized) epilepsy.

General Inclusion Criteria

- Subject is between 12 and 75 (unless studying a purely pediatric population; provided that rigorous prior studies have been done to suggest appropriate dosing for ages 12 and above).
- Ability to provide informed consent (or assent if under the age of 18)
- Ability to keep accurate seizure diaries
- Subject had prior neuroimaging with report available

Drug Resistant Inclusion Criteria

- Subject meets the 2009 ILAE definition of drug resistant epilepsy (Failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapy or in combination) to achieve sustained seizure freedom) (Kwan, 2010).

Focal Epilepsy Inclusion Criteria

- Fulfills criteria for a focal epilepsy (not, for example, Lennox-Gastaut with focal seizures).
- Clinical semiology should be described and fulfills criteria for focal seizures.
- Subject has no seizures that are not focal by the new ILAE criteria.
- At least some of the focal onset seizures should be observable [either a) without impairment of consciousness or awareness, with observable motor or autonomic components, b) with impairment of consciousness or awareness, or c) evolving to a bilateral, convulsive seizure (involving tonic and clonic components)].
 - Subject may also have non-observable seizures, but some of the seizures must be observable. An exception can be made for seizures that have no observable component but have been demonstrated to have an electrographic component on EEG.

Primary (Genetic) Generalized Epilepsy Inclusion Criteria

- Fulfills criteria for either a genetic or presumed genetic epilepsy or epilepsy of unknown cause (“idiopathic” in previous terminology).
- Clinical semiology fulfills criteria for the following generalized seizure types: typical absence, myoclonic seizures and generalized tonic-clonic, without other seizure types such as tonic and atonic seizures.
- Electroencephalogram (EEG) or report is available demonstrating either a normal background or generalized spike-wave of 3 Hz. If the background is normal, additional confirmatory evidence (eg family history) should be provided to confirm a primary (genetic) generalized epilepsy.

General Exclusion Criteria

- Subjects with significant progressive disorders or unstable medical conditions requiring acute intervention
- Change in AED regimen in the last 28 days
- Subject is currently taking > 3 concomitant AEDs
- Subject has had status epilepticus within the past 2 years
- Vagus Nerve Stimulation (VNS), Deep Brain Stimulation (DBS), Responsive Neurostimulator System (RNS) or other neurostimulation for epilepsy device implanted or activated < 1 year prior to enrollment, or
 - Stimulation parameters that have been stable for < 3 months, or
 - Battery life of unit not anticipated to extend for duration of trial
- Epilepsy dietary therapy initiated < 3 months prior to enrollment
- Epilepsy surgery < 1 year prior to enrollment

- Clinically relevant abnormalities in bloodwork detected (e.g. rising or new onset 3X liver function tests (LFTs)).
- Active suicidal plan/intent in the past 6 months, or a history of suicide attempt in the last 2 years, or more than 1 lifetime suicide attempt.
- A psychiatric disorder where changes in pharmacotherapy are needed or anticipated during the study
- Any condition that may impact a subject's ability to follow study procedures or subject's safety, based on what is known about the pharmacology/toxicology profile of the trial agent(s).

Drug Resistant Exclusion Criteria

- Time of onset of epilepsy treatment < 2 years prior to enrollment

Focal Seizures Exclusion Criteria

- EEG shows any pattern not consistent with focal etiology of seizures (e.g. generalized spike-wave)
 - Subjects with focal onset seizures which involve subjective sensory or psychic phenomena only, without impairment of consciousness or awareness, (formerly referred to as simple partial seizures without observable component), and no ictal EEG correlation with clinical symptoms.

Primary Generalized Seizures Exclusion Criteria

- The overall pattern of the EEG is not consistent with generalized onset of seizures (e.g. clear evidence of secondary bisynchrony mimicking a primary generalized pattern).

Discussion

Considerations for General Inclusion Criteria

Age—The working group recommended increasing the age window for certain “adult” trials to ages 12 through 75. The recommendation for increasing the upper age boundary is based on the fact that studies including older adults are desirable, and mortality in incident epilepsy for people aged 65–75 is not much greater than the general population². The group also recommended lowering the age window to 12 for adult trials of investigational agents for which adequate prior preclinical and clinical safety and PK studies have been done to suggest appropriate dosing for ages 12 and above (Crom 1994; FDA Guidance for Industry: General considerations for pediatric pharmacokinetic studies for drugs and biological products). (These data could be developed from studies in another condition.)

Informed consent: the proposed subject (or appropriate surrogate/caregiver in the case of children under the age of 18) must be able to provide informed consent or assent as appropriate (Declaration of Helsinki, 6th revision).

Seizure reporting—The proposed subject (or appropriate surrogate/caregiver in the case of children) must be able to keep accurate seizure diaries. The working group discussed the value of adding a requirement to demonstrate ability to keep an accurate seizure diary for three months prior to randomization, to minimize the likelihood of missing data. Ultimately, the group decided to recommend that individual studies establish trial-specific requirements.

Imaging—In general, epilepsy patients should have had neuroimaging as part of their prior clinical care. Magnetic Resonance Imaging (MRI) is strongly preferred, but Computed Tomography (CT) is acceptable where MRI is difficult to obtain or not available (Krumholz, 2007). Individual studies should specify the maximum timeframe for prior imaging studies in the protocol. At a minimum, the report should be available for review; individual studies should decide whether the scan is needed as well. (Note, in cases where imaging is typically not required (e.g. typical childhood absence epilepsy) investigators and sponsors may make a decision against including a prior imaging requirement.)

Women of childbearing potential—Study populations should be as representative as possible, so in general, the working group agreed that women of childbearing potential (including all post-menarche and pre-menopausal females) should be included in trials provided that they are protected from pregnancy while exposed to study drugs. The requirements for the degree of protection from pregnancy will depend on a number of factors, including whether it is known that the study drug(s) are potentially harmful to the developing fetus, or whether preclinical or other data have suggested that it would be safe. Women taking oral contraceptives should be counseled to use a double barrier method (one of the methods should be non-hormonal) if study drugs are expected to be enzyme-inducers, or if the woman is receiving an enzyme inducing AED as a background medication. The potential for selection bias as a result of indirect exclusion of younger female subjects who are reluctant to employ the double barrier method should be investigated in future studies.

²Mortality in the US population per 100,000:

Age	Mortality rates
55–64	877.7 (or 0.88%)
65–74	2,011.3 (or 2.01%)

SMR for death in people with incident epilepsy comparing the observed deaths to those expected based upon the age and gender distribution.

Age	SMR
55–64	3.0 (2.0–4.5)
65–74	1.5 (1.0–2.2)

Considerations for Drug Resistant Inclusion Criteria

Drug resistance—In studies of drug resistant patients (previously referred to as medically refractory) the working group agreed to adhere to the 2009 ILAE definition of drug resistant epilepsy (Kwan, 2010), which states:

- Failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapy or in combination) to achieve sustained seizure freedom.

The ILAE definition does not specify seizure frequency and the group agreed that it would not recommend any specific seizure frequency since this varies from study to study (e.g. focal vs. primary generalized seizures).

Considerations for Focal Seizures Inclusion Criteria

EEG—Individual trials should specify minimum criteria for the study.

Considerations for Primary Generalized Seizures Inclusion Criteria

EEG—The working group recommended that an EEG or report is available demonstrating generalized spike-wave. This requirement is an effort to reduce the misclassification of patients with focal onset seizures as generalized onset. If the EEG does not reveal generalized spike wave and the background is otherwise normal, there should be other available evidence confirming that epilepsy is generalized (see above).

Considerations for General Exclusion Criteria

Age of seizure onset—The working group recommended no exclusion for time of onset of seizures (e.g. no exclusion for seizures beginning after age of 60).

Race, ethnicity and sex—Although most trials already include subjects of all races and ethnicities, and both sexes, it is worthwhile to mention that there should be no exclusion solely on the basis of race, ethnicity or sex.

Chronic medical conditions—Subjects with stable medical conditions should be allowed to enter trials, as long as the condition would not interfere with the conduct of the trial, cause a known increase in risk of the intervention, or be expected to require additional health intervention during the course of the trial. Thus, for example, stable diabetes without significant organ damage should not be exclusionary. This approach will increase the generalizability of the trial and maximize recruitment. However, subjects with significant progressive disorders or unstable medical conditions should be excluded at all ages (e.g. an unstable arteriovenous malformations (AVM) at high risk of hemorrhage or requiring intervention would be exclusionary.)

Body Mass Index (BMI)—The group recommended no limitations on BMI or weight as a default. This was decided based on absence of clear reasons to exclude based on BMI, and the fact that subjects with a very high BMI are uncommon (Ogden, 2006). However, if there is a good pharmacokinetic reason to exclude on the basis of BMI, it should be stated. Individual trials could consider limitation on lower and higher end of body weight,

particularly if subjects are included to age twelve, and/or there is a pharmacokinetic reason to believe that exposure will be correlated with body weight (e.g. lipid solubility).

Change in AED regimen—The group recommended that subjects enrolling in trials should be on a stable AED regimen for at least twenty-eight days prior to entering the trial. A change in AEDs within the last 28 days is exclusionary.

Concomitant anti-seizure medication: the working group recommended exclusion of subjects currently taking more than three concomitant AEDs; an implanted VNS device or use of ketogenic dietary therapy should not be exclusionary in a subject taking 3 or fewer drugs. The group recommended that subjects who are on phenobarbital, primidone, or chronic benzodiazepines be included in trials unless there is a specific study-related reason to exclude those taking these drugs. Benzodiazepine derivatives used as sleep aids should not be counted as an AED, although the site investigator should ensure that the subject is not overly sedated or abusing medication, or would otherwise be a poor candidate for the trial.

Status epilepticus—Epidemiologic studies indicate that the highest risk of recurrent status epilepticus is within the first 2 years (Hesdorffer et al., 2007). Because status epilepticus is a rare and serious event, its occurrence in one arm of the trial could give the mistaken impression that it was caused by the intervention (or prevented if occurring in the placebo arm), which could confound interpretation.

Vigabatrin, ezogabine/retigabine or felbamate use—Use of vigabatrin, ezogabine/retigabine, or felbamate should not be a standard exclusion criterion. However, there are some specific trials for which it may be reasonable to exclude subjects who have been exposed to these drugs. For most studies it will be considered safe to include subjects who have been on felbamate for at least one year (aplastic anemia and hepatic failure usually occur within 6 months to one year), (Pellock, 2006) and subjects on or off vigabatrin with stable visual fields. Subjects on vigabatrin need to have been on vigabatrin for at least 2 years, as most visual field changes occur between 6 months and 2 years (Kälviäinen, 2001). Subjects on vigabatrin should have available, appropriate documentation of visual fields. Enrollment of subjects taking ezogabine/retigabine should be carefully considered since this drug has recently been found to cause retinal abnormalities of unclear significance (bluish discoloration; Manufacturer's prescribing information for POTIGA (ezogabine)). Also, some treated individuals have been noted to have visual acuity abnormalities, but it is not known if this is related to the drug and/or the retinal abnormalities. It is highly recommended that subjects who have been exposed to ezogabine/retigabine also have documentation of stable visual acuity and normal fundoscopy.

Rescue medication—Subjects who use intermittent rescue benzodiazepines should not be excluded from trials, since most frequently the benzodiazepine is taken after the occurrence of a seizure, so there should be minimal change in seizure counts. Use of benzodiazepines should be documented. Individual trials may wish to limit enrollment of subjects who use rescue medications if they might impact exit criteria, or for patients whose seizures tend to cluster, and for whom the use of rescue medication may be expected to substantially alter seizure counts.

Previous trial—Subjects who have participated in other drug or therapeutic device studies should not be excluded, as long as enrollment in the current trial is three months after the last dose of the previous agent, or last activation of the device.

Neurostimulation—Subjects with VNS, DBS, or RNS which has been implanted for at least one year, with stable stimulus parameters for at least three months, should not be excluded. Use of a magnet by the subject to trigger a device activation (as is available for VNS and DBS) should not be an exclusion criterion, as this occurs after or during a seizure and should not impact seizure counts (although it might change seizure type). The use of other neurostimulation devices or procedures, such as Transcranial Magnetic Stimulation (TMS), is currently considered experimental, and additional data is needed to assess implications for clinical trial enrollment. A preliminary recommendation is to exclude subjects who have been exposed to TMS less than three months prior to enrollment. The working group anticipates that more will be known about this emerging technology in the next several years so that a more definitive recommendation can be made.

Epilepsy dietary management—Subjects on the ketogenic or modified Atkins diets who have been on a stable regimen for a minimum of three months should not be excluded. Dietary therapies can be an exclusion criterion if there is a good pharmacokinetic reason for a particular novel AED (e.g. high fat diet may have an effect on AED absorption).

Epilepsy surgery—Subjects who have had epilepsy surgery more than one year prior to screening should not be excluded. If the subject has had radiosurgery, enrollment should be delayed until two years post-surgery.

Seizure free interval—The workshop participants did not recommend standard exclusion of subjects with prolonged seizure free intervals, since this will be study dependent.

Seizure rate—Although the group discussed whether there should be an upper limit of seizures per day (e.g. ten per day), it was decided that the only limit recommended should be the ability to accurately count the events. Subjects with uncountable seizures should be excluded. The exception to this would be scenarios for which “days with seizures” is an acceptable alternative, although the concern with this approach is that it could miss an increase in seizure clusters. In addition, a minimum monthly seizure rate is not specified in these guidelines, although studies have traditionally excluded subjects with fewer than 3 seizures per month. The ILAE definition of drug resistance does not specify seizure frequency and the group agreed that they would not recommend any specific seizure frequency since this varies from study to study (e.g. focal vs. primary generalized). It may also depend on study design.

Abnormal laboratory findings—The group recommended that only clinically relevant abnormalities in bloodwork (e.g. rising or new onset 3X LFTs) should serve as the basis for exclusion. Isolated serum gamma-glutamyl transpeptidase (GGT) elevation should not be a basis for exclusion (Whitfield et al., 1972). Chronic mild anemia or mild hyperglycemia should not be standard exclusion criteria.

Psychiatric comorbidities—Psychiatric comorbidities are present in up to half of subjects with epilepsy (LaFrance et al, 2008). The group recommended that subjects with major depression or subjects with only one prior suicide attempt should not be routinely excluded from trials. That is, subjects who have depression without the historical factors listed above should not be excluded. However, subjects who currently have a psychiatric disorder where changes in pharmacotherapy are needed or anticipated during the study should be excluded, and referred for appropriate clinical care. Additionally, subjects with active suicidal plan/intent in the past 6 months, a history of suicide attempt in the last 2 years, or more than 1 lifetime suicide attempt should be excluded and referred for clinical care. A screening question or validated questionnaire could be used to assess suicidality (e.g. Beck Depression Inventory-II Question 9 or the Columbia Suicidality Severity Rating). The DSM-5 notes that “individuals remain at higher risk for further suicide attempts and death in the 24 months after a suicide attempt” (APA, 2013). If there is a question about the stability or capability of the subject to comply with the trial requirements, the subject should be evaluated by a mental health professional prior to inclusion.

Other neurologic, psychiatric, or medical comorbidities—A subject with any condition that, in the opinion of the investigator, may significantly impact the ability to follow study procedures may also be excluded (e.g. dementia, recurrent unipolar depression, or mania, active psychosis, encephalopathy, current alcohol or substance related disorder, etc.). When considering enrollment of a patient with a prior history of substance abuse, investigators should consider the duration of abstinence; a longitudinal outcomes study demonstrated that more than 66% of individuals with 1 to 3 years of abstinence sustained it in the following year (Odds Ratio [OR] = 3.4, $p < .05$), and of those with 3 or more years of abstinence, 86% sustained it (OR = 11.2, $p < .05$). Women were significantly more likely than men to sustain abstinence following 1 to 3 years (75% vs. 54%), and 3 to 5 years (93% vs. 71%) (Dennis et al. 2007).

EEG parameters—In studies of focal epilepsy, the group recommended that studies do not include an EEG requirement so long as the subject’s clinical semiology fulfills criteria. However, observation of a pattern on the EEG that is inconsistent with focal epilepsy should be exclusionary. Subjects with focal onset seizures without impairment of consciousness or awareness involving subjective sensory or psychic phenomena only (formerly simple partial seizures with only subjective symptoms) should only be included if there is ictal EEG correlation for these manifestations. For studies of generalized epilepsy of genetic or presumed genetic etiology, EEG confirmation of 3 hz generalized spike-wave should be required, if there is no clinical confirmatory evidence of a generalized epilepsy. The group felt that this was necessary to confirm a generalized onset, since seizure semiology often does not provide sufficient data for confirmation of this syndrome. The subject should be excluded if the EEG is consistent with focal onset seizures. EEG should meet minimum standards and should include activation procedures or should be repeated. A statement of minimum EEG criteria should be indicated in inclusion/exclusion criteria for a given study.

ECG or Q-T interval: the group decided not to include a specific recommendation about ECG or Q-T intervals because these may be drug- and study-specific; however, if a cardiac issue is expected subjects should be evaluated prior to enrollment and possibly excluded.

Risk of SUDEP: the working group discussed the available data on the risk of sudden unexpected death in epilepsy (SUDEP) for clinical trial participants, but determined that at this time, it was not possible to specify an appropriate threshold for seizure frequency or other factors that would indicate subjects at high risk. As this data emerges, appropriate exclusion recommendations should be developed as part of a set of updated guidelines.

Considerations for Drug Resistant Exclusion Criteria

Duration of epilepsy—The working group recommended that in general, subjects with drug resistant epilepsy be entered no sooner than two years from time of onset of treatment. Although the data on this position are limited, the working group was concerned that within the first 2 years, the prognosis and course may not be known. Additional research needs to be done to confirm or refute the validity of this concern. Trials of subjects other than drug resistant epilepsy (e.g. new onset seizures) will have specifically tailored criteria based on study design.

Considerations for Focal Seizures Exclusion Criteria

The group recommended that subjects whose only seizure type is focal onset seizures without impairment of consciousness or awareness involving subjective sensory or psychic phenomena only (formerly simple partial seizures with only subjective symptoms) should be included only if there is ictal EEG correlation for these manifestations.

Considerations for Generalized Seizures Exclusion Criteria

The group recommended that a routine EEG at minimum be available to screen for focal epilepsy with secondary bisynchrony masquerading as primary generalized epilepsy.

Conclusion

These recommendations are intended as a starting point. Creation of single set of selection criteria that would be a perfect fit for every potential study in these populations is not possible. New compounds may have pharmacokinetic properties and safety concerns for different populations which dictate selection criteria that were not discussed above. Ideally, investigators will be encouraged to transparently discuss why each criterion was or was not chosen. This may be particularly helpful both at the outset of a study when neurologists are deciding whether or not to participate, and when trial results are reported in the medical literature.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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April 30, 2011 Workshop Participants:

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Highlights

- Adequate selection and enrollment of subjects is key to successful epilepsy trials
- Selection criteria must maximize scientific impact, safety, and ability to recruit
- Workshop attendees suggested guidelines for “default” criteria for epilepsy trials
- Criteria apply to regulatory trials in subjects with focal or generalized seizures