SPECIAL ARTICLES

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Ethical Issues in the Conduct of Clinical Trials in Obstructive Sleep Apnea

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Scientifically rigorous clinical trials are needed to test continuous positive airway pressure's (CPAP) effect on important clinical endpoints known to be associated with obstructive sleep apnea, such as myocardial infarction, cardiac arrhythmias, stroke, mortality, seizures, and cognitive function. In this "Special Article," we review the regulatory and ethical issues that surround the design and conduct of CPAP trials, including selection of the appropriate control condition, exclusion criteria, and follow-up duration.

Keywords: Obstructive sleep apnea, clinical trials, ethics

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The randomized, double-blind, placebo-controlled trial is the scientific gold standard to evaluate therapeutic interventions. Yet, for methodological, regulatory, health service, and ethical reasons, this standard of assessment is less readily applied to devices and surgeries. Three decades of research in the fields of breast cancer, carotid endarterectomy, and pulmonary artery catheters has taught us that despite observational studies, physiological rationales, and clinical acumen, treatments that have both benefits and risks (and significant costs) should be rigorously tested before they are widely promoted in clinical practice.

One of the critical issues in sleep medicine is whether treatment with continuous positive airway pressure (CPAP) can modify disease processes associated with obstructive sleep apnea (OSA), improve patient longevity, and prevent serious adverse outcomes. Here, the use of the randomized controlled clinical trial to evaluate CPAP in OSA presents a number of challenges including the identification of appropriate comparison and control groups. A number of different approaches have included delayed CPAP therapy, subtherapeutic ("sham") CPAP, best "alternative" therapy, or an inert oral placebo, each of which has specific strengths and weaknesses.

Without a suitable control group, key questions about the direction and effect size of CPAP on clinical endpoints (i.e., acute myocardial infarction, cardiac arrhythmias, stroke, death, seizures, and cognitive function), may not be adequately addressed. Those involved in the design and oversight of clinical trials must grapple with scientific and ethical considerations that are central to any clinical research in which a "failure to treat" could deny participants of potential benefits and result in adverse consequences. Although such ethical issues are often encountered by trialists, funding agencies, institutional review boards, and safety monitoring committees, no published guidelines are available that have been developed by the sleep medicine community. These issues were examined and debated in a 2-hour symposium held during the SLEEP 2009 23rd Annual Meeting of the Associated Professional Sleep Societies, LLC (APSS) in Seattle, Washington. The following report summarizes this discussion and panel conclusions on several key issues.

ETHICAL RULES AND REGULATIONS

In the United States, federal rules protect human subjects in federally funded research. These rules also are used by academic institutions to judge the acceptability of all human subjects research. Title 45 part 46 of the Code of Federal Regulations (45 CFR 46) requires that "risks to subjects are reasonable in relation to anticipated benefits" and that "risks to subjects are minimized." Thus, *the risks of being in a control group must be considered "reasonable."* This federal rule is based on the Belmont Report, a 1979 study commissioned by The Office of Health and Human Services.[1] Although Belmont did not specifically refer to the use of placebos, it did outline the basic ethical tenets of respect for persons, beneficence, and distributive justice. It also laid the foundation for a consent process that requires accurate description of the risks associated with participation in research.

The Declaration of Helsinki is an international document with rules for research. First adopted by the World Medical Association in 1964, the declaration has undergone several amendments, two of which are relevant to the use of placebos. "The benefits, risks, burdens, and effectiveness of a new

method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists" was added in 2000. A year later, the World Medical Association clarified that placebos may be used under certain circumstances when a proven therapy does exist. As part of a formal revision of the Declaration of Helsinki in 2008, the following provision was included: "The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option."[2]

Conclusion: Despite the wide availability and suitability of CPAP for OSA, a no treatment or non-therapeutic (placebo) comparison treatment is permissible if the rationale is compelling and deferral of CPAP does not pose excessive risks to participants.

CLINICAL EQUIPOISE

For a clinical trial to be considered ethical, several key requirements are widely considered necessary: qualified investigators, scientific value, scientific validity, just and non-coercive subject selection, favorable risk-benefit ratio, independent review, informed consent, and respect for potential and enrolled subjects especially those seen as vulnerable (such as children, prisoners, fetuses, and those with diminished capacity).[3] A concept that is central to these areas is that of *clinical equipoise*. Clinical equipoise exists when there is uncertainty within the expert scientific community about the relative merits of one or more treatment options.[4]

Based on the state of the science, equipoise for treatments of OSA is maintained for many important clinical endpoints. Although data are accumulating, they do not yet establish with certainty that CPAP for OSA reduces the risk for cardiovascular events such as stroke, acute myocardial infarction, sudden death, heart failure, or cognitive dysfunction and seizures. Despite the large and developed body of evidence of an association between OSA and cardiovascular disease,[5] no definitive trials demonstrate that CPAP treatment can prevent the occurrence of cardiovascular outcomes. Moreover, evidence of the effect of CPAP on surrogate cardiovascular measures such as blood pressure is conflicting. Taken together, three recent meta-analyses on the topic suggest modest effects (e.g., ~2 mm Hg resting systolic blood pressure reduction) from such treatment.[6-8] Greater effects may occur in those with more severe OSA and those who are more adherent to therapy.[8] Thus, given the uncertainty of effects on clinical endpoints and only modest effects on the intermediary measure of blood pressure, delayed treatment, or use of a placebo in a typical OSA patient with hypertension would not appear to violate ethical rules such as the Declaration of Helsinki. However, withholding CPAP for a long period in OSA patients with refractory or poorly controlled severe hypertension may represent an unacceptable level of risk.[9]

Evidence is most robust for effects of CPAP on excessive daytime somnolence and reduced quality of life,[10,11] at least in those with moderate or severe OSA,[12] so equipoise may no longer exist with respect to these outcomes for this severity of disease. Even so, as the use of a placebo (or no treatment) instead of CPAP may not result in serious or permanent harm, research with control groups would, in some circumstances, still be acceptable over the short term. Given that CPAP can improve reaction time and steering performance in driving simulations,[13] individuals who are at high risk of motor vehicle crashes, such as those with a recent near-miss or prior crash due to sleepiness, and those at risk for high impact crashes such as commercial drivers, might be excluded. The risk of a motor vehicle crash in an untreated OSA subject may be reduced by instructions to all trial participants to avoid driving when sleepy and education about signs of sleepiness.[14] However, data are not available to support the effectiveness of this approach or the ability of people to identify reliably when they become sleepy. Of course, this approach also introduces the potential for significant selection bias, given that patients without daytime sleepiness may not be equivalent to those with this symptom, in other ways besides the sleepiness.[15]

Another important consideration is that CPAP adherence is quite variable and many patients perceive CPAP to be uncomfortable. This is due in part to adverse effects of CPAP, including sleep disruption and nasal symptoms. This, in conjunction with the lack of a high level of evidence supporting the efficacy of CPAP for many outcomes, provides further justification for trials designed to assess critically the overall benefit of CPAP relative to its burden.

Conclusion: Given the need for clinical equipoise for many of the important treatment outcomes associated with OSA, randomized controlled trials are justified, with consideration given to special populations (e.g., commercial drivers, and those with a history of motor vehicle accidents or near-miss due to OSA-associated sleepiness).

INFORMED CONSENT

The patient-doctor-treatment relationships must be kept distinct from the subject-investigator-experimental study relationship. These roles can be conflated when a treating physician serves as the investigator. Subjects must understand that the clinical trial is not a treatment but rather research in which the intervention may help, harm, or do neither. Therefore, consent generally should be sought by a study team member other than the patient's medical care provider. In fact, the Declaration of Helsinki states that in the case of a doctor-patient relationship, someone other than the doctor should discuss the research and obtain consent in order to avoid confusion between treatment and research for the prospective subject. The consent process needs to consider potential benefits and risks, and alternative treatment strategies. Consideration of alternatives should include information on possible adverse consequences of untreated OSA and the ability to obtain CPAP off study. Patients may elect to participate knowing the risks for an identified poor outcome. This knowledge and consent to participate may help mitigate the negative consequences of delayed OSA therapy.

Conclusion: Efforts are required to ensure that patients are well informed of the consequences of clinical trial participation. Information should come from a knowledgeable source unconnected with the patient's care.

STUDY DESIGN

General Trial Design Strategies

Risks of delayed treatment with CPAP may well be small during a short-term period of observation. Consequently, most controlled clinical trials of OSA have been less than 6 months in duration.[14,16-18] Moreover, such ongoing risks associated with participation are relatively small when considered against the potential wider societal and scientific benefits of such research that provides new data on important outcomes. Additionally, some countries and some US labs have waiting lists for sleep studies that are several months to a year in duration. In these settings, intervention delays of similar lengths may not impose any potential risks worse than those that would be encountered in the course of standard clinical practice.

Alternatives to the traditional parallel group study design have been proposed to avoid randomization to placebo or delayed treatment, but none are scientifically sound to assess the effects of long-term CPAP on important outcomes such as myocardial infarction, stroke, or death. Studies that compare outcomes between patient groups who retrospectively proved adherent or non-adherent to CPAP do not eliminate important confounding variables that would otherwise be balanced with randomization. Open label trials raise the potential for patients to be managed differently by clinicians, depending on group allocation. Furthermore, subjects randomized to a no-intervention arm have the potential to cross over to CPAP if they have access to CPAP outside the study. Once informed of their diagnosis and the potential consequences that delayed treatment might engender, individuals may seek active treatment in a clinical setting. Given the high prevalence of OSA among certain high risk groups, one option is to randomize patients to CPAP or not without assessment of the subjects' OSA status. However, this may lead to considerable overtreatment and problems with poor adherence and drop-out. Finally, patients can be randomized to health care delivery bundles which include alternative approaches for screening and treatment. This design may be acceptable in situations where primary questions involve health service delivery issues, which include evaluation of alternative approaches for screening, diagnosis, and treatment. This is appealing since it is well known that the vast majority of patients with OSA are not diagnosed and treated, but raises questions regarding the comparative effectiveness of health systems with different approaches to OSA screening, diagnosis, and treatment.

Conclusion: The parallel group randomized controlled trial often provides the most rigorous and desirable method to assess benefits and risks of CPAP in OSA patients.

Control Groups

Several different controls can be used in CPAP clinical trials: sham CPAP, oral placebo, delayed CPAP, best medical therapy, and oral appliances. From a scientific standpoint, the ideal control would be entirely ineffective, and would preserve intervention masking of the participant, treating physician, and outcomes assessor.

A sham CPAP unit delivers less than 1 cm H_2O pressure at the mask. Sham CPAP is ineffective in the treatment of apneic events[10,19] and blood pressure,[20] appears to be a palatable intervention for subjects,[19] and is associated with a placebo effect.[21] Most published data on masking suggest that the study subject, investigator, and study coordinator are successfully masked.[17,22] While several studies have shown no difference in hours of use between control and active CPAP,[17,21-26] limited conflicting data also exist.[10] Objective measures of sleep quality such as sleep efficiency, total sleep time, and arousals are not altered by sham CPAP,[19,24,25] or are worsened to a small degree.[27] Nevertheless, some investigators involved in ongoing yet unpublished work question the tolerability and masking of sham CPAP.

Oral placebos have been used in studies,[28] but to some extent this implies deception to subjects, who are told a mistruth, that the oral placebo may improve sleep through its effects on the airway. This contrasts with a sham trial, where the subject is told that he or she has a 50% chance to receive a device that is designed not to have any positive or negative effect.

Delayed CPAP may be particularly useful as a control condition when treatment is challenging; this may occur based on the age group or comorbidity under study, or when the natural course of the untreated OSA includes the possibility for spontaneous amelioration. For example, in most children with OSA, part of the etiology is adenotonsillar hypertrophy that in many cases regresses with age, to the extent that half of habitual snorers no longer snore habitually one year later.[29] In an ongoing randomized controlled trial to determine whether childhood OSA contributes to neurobehavioral morbidity, expedited adenotonsillectomy is compared to 6 months of watchful waiting that includes minimal medical support in the form of nasal saline rinses.[30]

Other types of controls include best medical therapy alone or other OSA treatments that are typically less effective than CPAP, such as oral appliances. These non-placebo controls have the disadvantage that they cannot be masked. In these open trials, it is important that the assessment of outcomes is undertaken in a blinded manner. Nonetheless, the patient and treating physician will be aware of the study assignment and may implicitly act differently. For instance, the patient randomized to CPAP may feel "special" and therefore perform other healthful activities, or the physician may subconsciously treat a patient more aggressively. Use of a presumably less effective therapy as a control reduces some of the concerns raised by untreated OSA. However, this advantage often seems counterbalanced because the positive effect, even if limited, of the control over that achieved by placebo increases the required sample size and thus exposes even more subjects to an intervention that may be less effective than the primary active intervention.

Conclusion: Sham CPAP or no-treatment is often the best comparison (control) intervention to use in randomized controlled CPAP trials.

Limiting Potential Risks of Controlled Trials: Exclusions Based on OSA Severity and Limitations in Clinical Trial Duration.

Patients considered at the highest risk for complications from untreated OSA may be excluded from controlled CPAP trials.

A physiological basis exists to hypothesize that those with severe OSA may be at a higher risk. For example, trend analysis has shown that the risk of stroke and death increases with an increasing apnea-hypopnea index (AHI).[31] However, investigators remain uncertain that the exclusion of these severe OSA patients is always necessary, and if it is, no information dictates a specific threshold of AHI or minimum O_2 saturation. To exclude subjects, some investigators have used an AHI cutoff of 50,[17] an oxygen saturation below 75% for > 10% of the diagnostic study or 25% of the first 4 hours of the study,[14] or > 10% of the night with an O_2 saturation < 80%.[32] However, these criteria were selected without firm evidence. If the goal is to expose the fewest OSA patients to placebo for the shortest amount of time, the exclusion of patients at the highest risk of the trial endpoint will counterproductively necessitate a compensatory increase in the trial sample size.

Limiting the period of randomized intervention should reduce potential risks of OSA non-treatment. The minimal duration of a trial should be determined by the outcome. For example, in NIH-funded trials that address non–sleep related diseases, such as epilepsy, in which frequency of outcomes are likely to manifest over relatively short durations, patients have been randomized for two months.[17] A trial of neurocognitive outcomes in an adult OSA population had a six-month follow-up period,[14] while a stroke recovery study had a follow-up period of three months.[16] Similarly, a trial of children with OSA randomizes subjects for six months.[30] In contrast, outcomes such as incidence of stroke, myocardial infarction, or death, all of which have relatively low rates even among high-risk patients, may require that large numbers of individuals be followed for a number of years. Because of this, the ongoing international Sleep Apnea cardioVascular Endpoint (SAVE) study maintains patients at high risk for cardiovascular disease on randomized treatment for 3-5 years.[32]

Conclusion: The inclusion and exclusion criteria and duration of follow-up must depend on study objectives and risks to the subject.

ENROLLMENT OF PATIENTS IN RESOURCE-RESTRICTED ENVIRONMENTS

Special considerations are necessary for clinical trials that are conducted in developing countries or other resource-restricted environments by investigators or agencies in developed countries. In many of these settings, patients are not screened or treated for OSA as part of routine clinical care. Therefore, clinical trial participation may provide direct benefits, such as free access to assessment, monitoring, or therapy. Such benefits enhance risk of coercion, as subjects may decide to enroll solely to obtain medical care not otherwise available to them.

International clinical trials are governed by ethical codes, such as the Declaration of Helsinki, and by regulatory standards such as the guidelines of the Council for International Organizations of Medical Sciences (CIOMS),[33] an affiliate of the World Health Organization, and the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP).[34] Laws, regulations, and guidelines that govern human subjects research in 96 countries are listed by the US Department of Health and Human Services.[35] In the United States, regulatory standards include 45 CFR 46, 21 CFR 50, and 21 CFR 56. The FDA's 2008 decision that foreign clinical studies do not have to be performed under the principles of the Declaration of Helsinki, but rather that they should comply with GCP,[36] allows for the use of placebos even when proven interventions have been established.

The CIOMS dictates that "Before undertaking research in a population or community with limited resources, the sponsor and the investigator must make every effort to ensure that the research is responsive to the health needs and the priorities of the population or community in which it is to be carried out," and that "any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population or community." Placebos may be used "when there is no established effective intervention," "when withholding an established effective intervention would expose subjects to, at most, temporary discomfort or delay in relief of symptoms," and "when use of an established effective intervention as comparator would not yield scientifically reliable results and use of placebo would not add any risk of serious or irreversible harm to the subjects." CPAP trials should be justifiable given these rules. The use of a placebo when an effective intervention is established but just not available in the host country is called "ethically controversial."[33]

International controlled CPAP trials that include developing countries are ongoing. For the SAVE trial, where multiple sites in China and India are included, the study management team sought guidance from the Nuffield Council of Bioethics report.[37] The following criteria have been applied to the conduct of SAVE: the disease being addressed (i.e., OSA) is relevant to the host country's population; local expertise in sleep medicine is being developed; institutional review board or ethics committee approvals are obtained in both the host and sponsoring countries; site payments were determined not to be excessive in consultation with local communities; and the standard of care for the control group was determined in conjunction with local experts. A priori plans have been made to make CPAP ongoing in the intervention arm and available to the control group, should the results prove positive at the end of the study.

Conclusion: The extension of clinical trials into low resource settings requires the application of ethical standards to ensure that subjects are not exposed to unnecessary risk or coercion, and that health care resources are allocated and developed appropriately.

QUANTITATIVE METHODS ISSUES

As with the design of any clinical trial, sample size calculations are needed to estimate the appropriate number of patients, maximize the chance to identify the minimum clinically important difference, and limit unnecessary exposure of subjects to risk. If the trial is underpowered, then subjects are exposed to risk without the opportunity to contribute maximally to science. If too many subjects are enrolled, then some are subjected to the inferior treatment arm for no purpose. Interim analyses can allow a trial to be stopped early for futility based on a priori stopping rules, and can be used to stop a trial for harm. Interim analyses should be pre-planned and performed in a way to preserve types I and II error. Interim results and safety data should

be reviewed by an independent data safety and monitoring board that is charged to make any necessary recommendations including the need to terminate the study early. Additionally, it may be prudent to have a physician-observer ("safety officer") who is blinded to each subject's treatment, and whose primary responsibility is to ensure the subject's safety throughout the trial. Trial efficiency should also be maximized through consideration of appropriate outcome measures and analytic plans.

With concurrent CPAP clinical trials, results of one trial may be published while others are ongoing. If appropriate, new information should be introduced into the consent form and subjects undergoing study interventions may need to be reconsented. Under some circumstances, such as newly published compelling results in the same population under study, an ongoing trial may need to be concluded prematurely if equipoise no longer exists or if the benefit-risk ratio is no longer maximized.

Conclusion: Clinical trials require detailed and evolving methodological planning, and must be conducted with independent oversight by a data and safety monitoring committee.

SUMMARY

Given robust associations between OSA and important medical morbidities, well-designed CPAP intervention trials with relevant clinical endpoints are critical in order to prove cause-and-effect relationships in a definitive manner that can have maximal impact on treatment guidelines and human health. As the consequences of OSA in the short term, such as excessive daytime somnolence, are thought to be largely reversible and manageable with adequate safety precautions, the use of controls including placebos is ethically permissible when scientifically necessary to advance knowledge and health care delivery. When excessive daytime somnolence is not an exclusion criterion, subjects should be warned not to drive when sleepy and those with a history of near-miss or actual auto crashes due to sleepiness and commercial drivers should be considered for exclusion. Control conditions are vital to the scientific integrity of clinical trials, and may differ depending on the specific trial, but sham CPAP and no-intervention controls offer clear advantages in many instances. Due to the complexity of ethical issues, consultation with the institutional review board and an ethicist should be considered during the design phase of CPAP clinical trials. In the future, after the first clear demonstration that CPAP reduces serious morbidity—beyond sleepiness that may be easier to address safely or accommodate for limited periods—ethical OSA trial design may well change unavoidably in a manner that will make demonstration of additional benefits, as critical as they may be, most challenging.

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