Evaluating Devices for Treating Epilepsy

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Summary: Purpose: Research into new implantable devices for treating epilepsy is expanding rapidly. Pilot studies suggest sufficient safety and potential efficacy to justify proceeding with larger scale clinical trials. Understanding the challenges presented by these trials, the testing and approval process for implantable devices, and how these differ from requirements for antiepileptic drugs (AEDs) is vital to evaluating when and where these new technologies will fit into the therapeutic armamentarium.

Methods: Important lessons regarding the limitations of uncontrolled pilot studies, patient registries, and how the Food and Drug Administration (FDA) approval process can influence trials are drawn from the implantable device literature. Some discussion of the role of animal experiments is presented, both as justification for investigational device exemptions and their potential role in establishing safety. Clinical trial experience with the vagal nerve stimulator, the first device approved for the treatment of epilepsy, is also discussed.

Results: New implantable devices hold great promise for medically refractory epilepsy patients who have no other therapeutic alternative. If effective, they may become a viable alternative to epilepsy surgery or multiple AED therapy in appropriate patients.

Conclusions: The proper evaluation, use, and acceptance of antiepileptic devices will ultimately depend on carefully executed clinical trials that take into account unique aspects of these devices, such as the requirement for surgery, electrode placement, and navigation through FDA-monitored testing and approval. Key Words: Epilepsy—Devices—Clinical trials—Stimulator—Implantable.

There has recently been an explosion of research into implantable devices for treating epilepsy. This is largely due to the dramatic success of deep brain stimulation for movement disorders such as Parkinson’s disease and tremor (1), as well as a push to emulate the success of intelligent cardiac devices, such as pacemakers and implantable defibrillators (2). Brain stimulation for movement disorders modulates network function by inhibiting activity in deep brain nuclei via high-frequency electrical stimulation (≥130 Hz) (3). Different from epilepsy, the functional anatomy of these networks has been carefully mapped in experimental disease models in primates (4,5), and the effects of discrete lesions in these circuits is well known. In contrast, comparable circuits involved in seizure generation appear to be far more complex, particularly given the heterogeneity of epilepsy. Their functional anatomy and the effect of lesion experiments in models proven to be comparable to the human condition are not yet known, and the relevance of specific animal models to human epilepsy remains a subject of intense debate (6,7).

The expanding use and marketing of the vagus nerve stimulator (VNS) following its FDA approval has played a vital role in the development of devices for epilepsy, as it is the first of these technologies to garner widespread public acceptance for treating seizures. There are two major physiological paradigms that continue to guide device interventions in the brain aimed at arresting or preventing seizures: (a) modulation of abnormal cortical activity by exciting or inhibiting central structures such as the thalamus and brainstem, and (b) intervening directly in the region of the epileptic focus. The first group of devices, which includes thalamic stimulators and likely the mechanism of action of the VNS, was conceived, in principle, by Penfield and Jasper in the 1940s and 1950s. They coined the term “centroencephalon” (8), a central area that controlled seizure propagation or generalization. These pioneers put forth the idea that disrupting function in this region could somehow prevent seizure onset and/or propagation. This notion continues to enjoy support, now 40 years later, with observations that seizures in animal models of epilepsy likely start and propagate through discrete circuits (9,10). Better tools for physiological recording and functional mapping now allow investigators to map regions over which these central areas exert control. For example, the anterior thalamic nuclei (ANT) are hypothesized to modulate epileptiform activity in frontocentral cortex and the anterior temporal brain regions that are functionally connected to them. This notion is supported...
by pilot data suggesting that electrical stimulation in ANT may be most effect in modulating partial seizures arising from these regions (J. Kerrigan et al., unpublished observations; 11). Other central targets of interest in modulating clinical seizures include the centromedian thalamus, subthalamic nuclei, caudate nuclei, and the hypothalamus (12–18).

The second treatment paradigm focuses on delivering therapy in the regions where seizures begin, the ictal onset zone. The era of modern epilepsy surgery, aided by vastly improved structural and functional neuroimaging and high-fidelity intracranial ictal recording, has proven that partial onset seizures can be controlled or eliminated by intervention at the site of seizure onset. These interventions have, until recently, consisted primarily of focal cortical resection (19). More recently, other focal interventions, such as electrical stimulation, focal cooling, and localized drug infusion, have been demonstrated to stop seizures where they appear to begin (20–27). These observations suggest that seizures arising focally from the cortex are likely sustained and modulated by circuits connecting both local cortical and central functional areas, each capable of promoting or inhibiting seizure onset and propagation. These two approaches form the conceptual foundation for therapeutic devices for epilepsy currently under development.

**DRUG TRIALS VERSUS DEVICE TRIALS**

There are important differences between clinical trials of medical devices for epilepsy and antiepileptic drugs (AEDs). For most AED trials, delivery of drug is measured by dose and serum blood level. Dose ranges vary but are similar across patients, duplicate placebo-controlled trials are the gold standard, and increased efficacy is usually associated with administration of more drug, usually up to some threshold or bounded by symptoms of toxicity. With devices, there is no electrical counterpart to serum AED level, as stimulation amplitude, distribution, and perhaps even stimulation parameters such as frequency, pulse-width, and duration may vary from patient to patient. Duplicate device trials have historically not been required. Placebo controls are usually not possible, given the need for surgery and its inherent additional risk. Efficacy in device trials is usually measured against standard treatment, historical controls, or “active” controls. With active controls the device is set to deliver very low dose therapy, which is hypothesized either to be ineffective or to have little impact on seizures compared to full dose therapy, so that a dose–response effect can be demonstrated. Outcome measures from AED trials, such as percent reduction in number of seizures over treatment phases of several months, may not be sufficient for measuring device effects. Previous studies of stimulation devices indicate that much longer periods of time may be required for therapeutic effects to become evident or to “wash out” in therapeutic trials (28,29). In addition, specific outcome measures other than number of seizures, such as number of falls and injuries, for example, may be better measures of efficacy than seizure number in some populations, given the circuit-specific “local” therapeutic effects of stimulation in some central regions (J. Kerrigan et al., unpublished observations). Another very important difference between AED and device trials is the perceived amount of positive response required to judge device therapy to be effective. While typical AED trials of drugs that then successfully enter the marketplace have 50% responder rates of 20–35% on average, this type of efficacy may not be sufficient for implantable devices, depending on the morbidity and perceived risks of implantation. For peripherally implanted devices, such as the VNS, this perceived risk is low, and this level of device performance has generally been accepted by the physician and patient communities. For other devices that require intracranial implantation, caregivers and patients may require significantly greater efficacy before endorsing this therapeutic option. Finally, the issue of indemnification has become important in the area of device trials. Typically, the responsibility for indemnifying investigators against severe adverse outcomes has been assumed by companies sponsoring trials or the academic institutions where trials have taken place. Since risks of severe disability and death, while low, may be theoretically elevated compared to AED trials, universities and medical device companies have been reluctant to provide this coverage for implantable epilepsy device trials at the time this article is being written. This has typically not been a significant issue for AED trials.

**EARLY STUDIES AND CHALLENGES**

Implantable devices for treating epilepsy, primarily through electrical stimulation, have been the subject of clinical trials since the 1970s. Among the first efforts were those by Cooper et al., applying electrical stimulation to the cerebellar hemispheres (30–32). Despite multiple “open” uncontrolled trials, which indicated efficacy, two later placebo-controlled studies suggested little benefit (33,34). It is important to note that, based on early trials, this device obtained FDA approval and hundreds of the devices were implanted over the following years, many for indications other than epilepsy, for which approval was granted. A review of the clinical literature in cerebellar stimulation suggests that there is likely some efficacy in modulating seizures, although relatively mild. The device is now rarely implanted for treating intractable epilepsy, given the need for intracranial surgery and a relatively high perceived risk/benefit ratio. Two particular difficulties primarily encountered in these early trials: (a) lack of ability to discern if the intended amount of electrical stimulation was actually delivered to the target.
tissue; and (b) equipment failures, specifically in stimulator leads, batteries, and other parts of these devices (35). These types of problems in clinical device trials were later addressed in the Medical Device Amendment (MDA) of 1976. In addition to control and trial design issues, because it was difficult to discern whether or not the device was actually functioning properly or delivering the proper amount of stimulation after implantation, results of early trials are not completely clear. More rigorous requirements for component performance, safety, and reliability, as well as a more intensely regulated approval process, have made these types of problems much less common in the device world.

Another stimulation site, for which there is still considerable debate over efficacy in modulating seizures, is the centromedian (CM) nucleus of the thalamus. Pioneering pilot clinical trials by Velasco et al. (12,36–38) suggest efficacy of focal stimulation in this region for suppressing focal and generalized seizures. A rigorously conducted, blinded, controlled crossover study in seven patients showed only a modest benefit in reduction of generalized tonic-clonic seizures (30% reduction from baseline compared to 8% reduction from baseline with placebo), but not in total number of seizures (13). One problem in this study, which has also plagued similar studies, is the potential delayed or persistent effect of stimulation and its relationship to the study’s crossover design. Fisher describes one patient who became seizure free during stimulation and then did not resume having seizures after the “washout” period or into the “stimulation off” portion of the trial (13). This patient was reported as having a negative response because there was not a significant difference in outcome measures (for example, seizure frequency) when the “stimulation on” and “stimulation off” periods were compared, even though the patient became seizure free. This, coupled with a ≥50% reduction in the number of seizures in three of six patients in the open treatment phase, after conclusion of the study, clouds the interpretation of results. One way of looking at these results suggests that a larger trial may have clarified these issues, although there are still trial design problems, which were not apparent until this initial controlled pilot study was performed, that would have to be worked out. One central issue creating this problem is that the latency from onset of stimulation to maximal effect, and from cessation of stimulation to baseline, is not known. Pilot data suggest that this time period could be measured in months. Velasco and colleagues continue to investigate CM stimulation in other forms of epilepsy. The author is not aware of any ongoing controlled trials of CM stimulation in partial epilepsy at this time. Again, there is evidence, even from Fisher’s controlled trial mentioned previously, that CM stimulation has some efficacy in treating partial onset epilepsy. However, because of the lack of convincing controlled trial data, many investigators feel that this efficacy may be too small or specific to certain seizure types to gain broad acceptance in the epilepsy community or be successful in the medical marketplace.

Most recently, VNS has been shown to be of benefit in both open and controlled trials (39,40) and has been approved for use in epilepsy by the FDA. The mechanism of action of VNS remains unclear, but it is thought to work via the vagus nerve’s inputs to deep brain structures in the brain stem and diencephalon. VNS has been shown to increase metabolic activity in thalamus (41), thus possibly linking this newer technique with older approaches. Because of its importance as the first widely accepted implantable therapeutic device for epilepsy, a more in-depth discussion of the VNS is covered in the following sections.

Two other recent approaches to brain stimulation to abort seizures are in pilot clinical testing; both approaches are based on the idea to deliver electrical stimulation directly at the site of seizure onset. In one approach, stimulation is reactive, delivered after detecting seizure onset on the intracranial EEG. This has been reported under manual control after inducing afterdischarges during function brain mapping (42,43). In a natural extension of this approach, there are early reports of reactive stimulation in response to automated detection of seizure onsets and seizure precursors in patients implanted with intracranial electrodes using a bedside implementation of an implantable device (26). Proving efficacy in responsive stimulation trials is not encumbered by persistent effects of chronic stimulation, crossover design, or washout periods. These studies present their own set of challenges, such as the need for randomizing stimulation in response to event detection to prove a causal link between stimulation and events that follow (for example, “Would the event that triggered the detection have really become a seizure?” and “Would the stimulation have stopped it?”). The second method consists of direct stimulation of the epileptogenic zone, tested so far only in the hippocampus and mesial temporal lobe in patients with indwelling depth electrodes to suppress seizures (25,27,44). These pilot trials must address the same trial design issues as other more central forms of continuous or cyclical brain stimulation. In addition, they must address the possibility that seizure frequency may be decreased for some time, compared to baseline, after epilepsy monitoring and/or surgical placement of electrodes.

**CLINICAL TRIAL DESIGN AND CONSIDERATIONS**

Clinical trials to prove safety and efficacy of implantable devices to treat epilepsy must be viewed in the context of the FDA approval process. Without FDA approval, clinical trial data alone would be insufficient to help bring treatments based on these technologies to patients, and actual clinical testing would not be possible.
At the very least, this is due to the need for strict technical standards and control of component performance, reliability, and design for electrical devices, as well as the need for independent third-party scrutiny of manufacturer claims and trials. The nature of device trials is somewhat different from those standard for AEDs. Blinded, randomized designs are often not practical, given the need for surgical implantation of devices and the generally unacceptable risk tied to the idea of “sham surgery” for those in the “control” group. Rather, trials of medical devices are usually based on comparison to standard medical therapy or historical controls. Given the invasiveness of device implantation, results, in general, must be sufficiently good to justify the surgical risk and the considerable expense of this therapy. For this reason, in the area of epilepsy, it is likely that perceived efficacy requirements will be higher for devices that require intracranial implantation compared to those that exert effects through the peripheral nervous system. When devices can safely be turned on and off without harmful clinical effects, or symptoms that may “unblind” investigators and subjects, randomization to treatment and nontreatment periods is central to these clinical trials. As noted previously, the long half-life of stimulation effects, either positive or negative, is a factor that can potentially complicate these studies and might confound trials based on a crossover design. Different from AEDs, there is usually no equivalent of serum drug levels, which might identify a specific “dose” of therapy actually received by the target tissue or help define the length of any “washout” period. While it is possible that detailed physiological studies in humans or animals may answer these questions, these types of experiments have yet to play a significant role in human clinical trial design for these devices.

An excellent review of the FDA process, with regard to medical devices, can be found in a three-part article by Monsein in the journal Radiology (45–47). The FDA process for medical devices begins with determining the “class” of the device, either I, II, or III. As part of this classification, new technologies are also reviewed in the context of preceding inventions, referred to as “predicate devices,” to see whether they are “substantially equivalent” to them or not. Class I devices, such as toothbrushes and dental floss, are ones that are not life sustaining and do not present potentially life-threatening conditions. They pose little risk of injury to the user. Class I devices are ones in which a set of “general controls” or rules are sufficient to regulate their safe and effective use, for example, having circuitry that adheres to standard safety requirements. Class II devices, such as arterial catheters and monitoring devices, may be associated with significant risk in their use, but typically are not life sustaining or solely responsible for preventing life-threatening conditions. In addition to general controls, their use is governed by performance standards that “…include provisions to provide reasonable assurance of (their) safe and effective performance.” These standards must also, when necessary, include provisions concerning “…the construction, components, ingredients, and properties of the device and its compatibility with power systems,” conformity to test results, and measurement of the performance characteristics and, “where appropriate, require the use and prescribe the form and content of the labeling for the proper installation, maintenance, operation, and use of the device (46,48).” Class III devices, such as cardiac defibrillators, pacemakers, and brain stimulators, support life, prevent life-threatening conditions, and/or are associated with significant risk in their use or implantation.

The approval process, which also governs clinical trials, is greatly dependent on the class of the device. Class I and II devices can receive expedited approval through what is called the “510k” process, which does not necessarily require a full-scale clinical trial. If the devices are found to be “substantially equivalent” to existing devices, particularly ones in use before the MDA of 1976, approval may be granted with relatively little new clinical trial data. This legislation greatly changed the regulatory process for implantable devices. If Class I and II devices are not substantially equivalent to other previously approved or existing devices, they still are approved through the 510k process, but safety and efficacy must be proven anew. Class III devices must go through a lengthier and more involved approval process called “premarket approval,” or PMA, unless they are substantially equivalent to a “predicate” Class III device for which the FDA has not yet requested or approved a PMA (for example, a device approved before the MDA of 1976 for which a PMA has not yet been requested). The FDA has stated that it will eventually request PMA applications from all Class III devices, even those marketed before MDA legislation in 1976.

The PMA process is lengthy, and for new devices usually begins with an investigational device exemption (IDE) granted by the FDA to either perform a conclusive clinical trial to prove safety and efficacy or, more commonly, a “feasibility study” to see whether or not it is likely that a new technology will be safe and effective. IDE approval is dependent on a clear presentation that the potential benefits of the device far outweigh the risks of its experimental use, and that study centers’ Institutional Review Boards (IRBs) will grant approval to the studies. Potential benefits are often presented in the form of animal studies proving important principles (for example, seizure suppression in response to stimulation in a certain region). In rare cases when IRBs all agree that an experimental study poses “no significant risk” to subjects, some studies may be conducted without IDEs. This type of approval is relatively rare for device studies, but may be used to gather important information that can then be incorporated into device designs. After feasibility studies, further IDEs may be pursued to conduct larger, more conclusive trials. Armed with
results proving safety and efficacy from these trials, device developers must fulfill a host of other requirements in their PMA applications before being granted approval. These include adherence to “good manufacturing practice” (GMP), which ranges all the way from design consideration to the production and reliability of all components, the function and testing of devices, and the processes for shipping, distribution, labeling, and handling defective materials, complaints, and adverse events. The PMA application is therefore a complete scientific and regulatory review that must demonstrate not only safety and efficacy, but also an intact structure for actually fabricating, marketing, distributing, and supporting devices so that the entire patient experience with the new product is safe and well supported. Companies granted approval after a PMA must also demonstrate capability to adhere to postmarketing regulations, such as tracking device reliability and performance over time and informing all recipients of any problems immediately, should they be found. Approval after a PMA application is in effect a license to market and distribute a product. A typical amount of time from filing a PMA application to approval is 3–4 years. It is important to note that PMA application approvals are indication specific, meaning that if the device is approved for the treatment of partial epilepsy for adults, for example, a separate application for generalized epilepsies may be required, as well as for children, although their filing would be vastly simplified.

All devices for treating epilepsy, either FDA approved or currently in testing, are Class III devices. The first of these devices was the cerebellar stimulator, which was granted approval via a 510K application. Review of this application found the device to be substantially equivalent to pre-1976 devices that had been used several years before that time. The date of this approval was April 4, 1979. The VNS received its first PMA on July 16, 1997 for adjunctive treatment for partial epilepsy in individuals >12 years of age. It is, at present, the only Class III device approved to treat epilepsy that is actively in use. Other devices, such as EEG machines (Class II), cortical stimulators for functional brain mapping (Class III), and implantable brain stimulators for tremor and Parkinson’s disease (Class III), have been approved, but not for use in epilepsy at this time. However, their approval for other indications is relevant to current epilepsy device development and indications and may be used as supporting information for their applications.

The VNS system has been tested via an FDA-guided process through IDEs first proving feasibility and suggesting safety and efficacy in open label use (30), then two multi-center, controlled trials to support the PMA application. In the first of these trials, labeled “E03,” the results were considered “promising,” but the number of patients tested was considered too small to grant approval (39,49). In a second, more comprehensive trail including 254 patients, labeled “E05,” seizure frequency in a 12- to 16-week baseline period was compared to groups randomized to low-intensity and high-intensity stimulation. Statistically significant, dose-related (stimulation intensity = dose) positive results were demonstrated in change in seizure frequency and number of individuals, with ≥75% reduction in seizures over the treatment period. These trials, E03 and E05, point out a number of specific challenges related to performing randomized, controlled device trials for epilepsy, such as how to handle control groups when stimulation can be clinically perceived, and when a component of therapy includes manual activation of the device “on-demand” by the patient. Additionally, since epilepsy device trials are invasive by nature, as they require surgery of some kind at this time, initial studies are usually conducted on very refractory patients. This immediately biases trial results against efficacy, as the subjects are patients who have proved refractory to other therapies, and presents the additional challenge keeping patient medications as constant as possible during the trial so as to avoid introducing confounding variables.

Comparison of the “open label” feasibility studies with the results of more extensive studies designed to prove safety and efficacy yields important insights regarding the potential pitfalls of overinterpreting pilot studies, which usually include only small numbers of patients. These caveats are particularly important in assessing open label trials of brain stimulation therapy for epilepsy that have not yet progressed beyond the initial IDE feasibility stage, such as centromedian thalamic stimulation (12,36,50), hippocampal stimulation (25,27,44), and anterior thalamic (11) and subthalamic nucleus stimulation (14, 51,52).

DEVICE STRATEGIES

Current devices for epilepsy may be divided into two types. “Open-loop” devices chronically modulate brain activity to suppress seizures through a “duty cycle” in which stimulation or another therapy is regularly switched on and off by an internal clock. “Closed-loop” devices are more complex devices that monitor physiological signals and trigger a therapeutic response based on changes in these signals. The VNS, and devices that chronically stimulate the cerebellum and thalamus (for example, stimulators for tremor and Parkinson’s disease), are open-loop systems. Vagus nerve stimulation is sometimes triggered manually. The patient can activate the device when he or she feels a seizure beginning by moving a powerful magnet worn on the wrist over the implanted device. Thalamic stimulation applied to a variety of targets, as mentioned previously (CM, subthalamic nucleus, ANT), is currently being tested in pilot trials, under IDEs, using implantable devices already approved for use in patients with tremor and Parkinson’s disease. As noted previously, if effective,
these devices will still require PMA applications to gain approval for treating epilepsy because it is a new indication. Other devices, designed for both direct cortical and subcortical stimulation, are in early feasibility trials. These more complex devices also require multiple levels of approval before they can go into FDA-sanctioned use. For example, closed-loop devices require approval both for the algorithms that control device function, such as seizure detection or prediction logic, and for the therapeutic components of the device.

Designing, conducting, and interpreting clinical trials of new devices for epilepsy will present a number of challenges. As mentioned previously, overall change in seizure frequency may not alone be a sufficient outcome measure when judging efficacy. When devices trigger therapy close to seizure onset on EEG, secondary measures of efficacy may be needed, such as seizure duration, severity, rate of injury, or falls, in addition to symptoms, side effects, and complications, including those associated with surgery. Seizure prediction devices will need special attention to clinical trial design, given that a false-positive activation may have the same clinical result as an effective true positive activation—no seizure. Acceptable false-positive and false-negative detection, prediction rates for closed-loop devices, in addition to the consequences of intervention, will need to be interpreted in the context of side effects of brain stimulation. For example, if no adverse effects are associated with local brain stimulation to abort seizures, then achieving very high sensitivities at the cost of high false-positive triggering rates may be acceptable. If intervention is associated with side effects or increased risk of tissue injury, then more stringent algorithm performance criteria may be required. In either case, it will be necessary to develop novel statistical methods to deal with the uncertain effects of individual stimulations so that they can be viewed in terms of the bigger picture, whether or not the actual seizure frequency, severity, or resulting complications are reduced.

**THE ROLE OF ANIMAL RESEARCH**

Proving safety and efficacy of candidate devices for epilepsy through well-defined clinical trials in humans is the main goal of current device research, and a big focus of industry efforts in this area. An important question to ask as these pilot and more definitive clinical trials move forward is “what is the role of animal research?” Perhaps different from AED trials, there is no absolute requirement for animal-based research in the development of clinical devices for epilepsy. Historically, animal experiments have been used for “proof of principal” in central stimulation to modulate seizures. This body of work is discussed in detail elsewhere (2). Aside from these early experiments, which provided evidence that electrical stimulation can modulate seizures, most of the important work to date has taken place in human pilot trials. This is for two major reasons: (a) it is not clear which, if any, animal models of epilepsy sufficiently represent human epilepsy to the point where they can be used as more than proof of principal for efficacy experiments; and (b) there is already modest to considerable experience in central and cortical human brain stimulation to suggest that human pilot trials are reasonably safe. For example, subcortical stimulation has been proven safe and effective in treating movement disorders, and pathological examination of chronically stimulated subcortical tissues show no evidence of significant aberrant sprouting or more than minimal local gliosis (53–55). In addition, IDEs and IRB approval for human trials of cortical stimulation have been approved for pilot studies based on experience using cortical stimulation for functional brain mapping in the operating room and in patients implanted with subdural electrodes during evaluation for epilepsy surgery (56). Some information does exist regarding potential effects of chronic, continuous hippocampal stimulation in humans, consisting primarily of basic examination with light microscopy, but there is considerable interest in acquiring more pathological data, given experience with kindling models of epilepsy in animal models (44).

Given this considerable experience with human brain stimulation and pilot studies, it is not clear that animal experimentation will initially play a great role in bringing new brain stimulation devices into large-scale clinical trials. They will certainly be instrumental in helping perfect second generation devices and determining the mechanism of action of focal brain stimulation. They may even have a significant role in long-term safety studies, although it is not clear how one might interpret changes such as mossy fiber sprouting in a rodent subjected to continuous cortical, hippocampal, or amygdalar stimulation analogous to human stimulation trials currently under way. Given the disparity between kindling in rodents and primates (it is much more difficult in the latter), it may be that only pathological examination of human tissue resected after clinical trials of stimulation may be sufficient to definitively answer these questions (57). Along these lines, some study designs are being considered in which patients who are good candidates for temporal lobectomy are randomized to undergo a trial of focal brain stimulation in the region to be removed at the end of the study. More debate on this topic is sure to follow as clinical trials of implantable epilepsy devices move forward. The previous discussion is intended more to clarify important questions in this area rather than to promote a particular point of view.

**SUMMARY**

In summary, researchers, device manufacturers, experts in clinical trial design, and government regulators are
working closely together to develop standards and appropriate trial designs to test the safety and efficacy of new technologies for treating seizures, and to bring promising new devices for epilepsy to patients and the marketplace. Important trailblazing in this area related to the VNS and similarly principled cardiac devices provide precedents for appropriate clinical trials. Experience with brain stimulation for movement disorders and cortical stimulation for function brain mapping related to epilepsy surgery have pushed antiepileptic devices solidly into human trials, with comparatively little supporting animal experimentation. While similar to AED trials, clinical trials of implanted devices require special consideration, which necessitates that the epilepsy community participates actively in this process, particularly in the design and interpretation of clinical device trials. A burning desire to help refractory patients, and the desperate need for new therapies, must be balanced by deliberate care and healthy skepticism to insure the safety and efficacy of new devices. All who are involved in perfecting antiepileptic devices, particularly epileptologists, will need to insure that the results of clinical trials support appropriate treatment indications, and that the risks, side-effect profiles, and practice parameters governing the use of these exciting new therapies are optimized to best treat and protect our patients.

REFERENCES


