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Spinal Cord Stimulation Versus Re-operation in Patients With Failed Back Surgery Syndrome: An International Multicenter Randomized Controlled Trial (EVIDENCE Study)

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Objective: This paper presents the protocol of the EVIDENCE study, a multicenter multinational randomized controlled trial to assess the effectiveness and cost-effectiveness of spinal cord stimulation (SCS) with rechargeable pulse generator versus re-operation through 36-month follow-up in patients with failed back surgery syndrome.

Study Design: Study subjects have neuropathic radicular leg pain exceeding or equaling any low back pain and meet specified entry criteria. One-to-one randomization is stratified by site and by one or more prior lumbosacral operations. The sample size of 132 subjects may be adjusted to between 100 and 200 subjects using a standard adaptive design statistical method with pre-defined rules. Crossover treatment is possible. Co-primary endpoints are proportion of subjects reporting ≥50% leg pain relief without crossover at 6 and at 24 months after SCS screening trial or re-operation. Insufficient pain relief constitutes failure of randomized treatment, as does crossover. Secondary endpoints include cost-effectiveness; relief of leg, back, and overall pain; change in disability and quality of life; and rate of crossover. We are collecting data on subject global impression of change, patient satisfaction with treatment, employment status, pain/paresthesia overlap, SCS programming, and adverse events.

Discussion: As the first multicenter randomized controlled trial of SCS versus re-operation and the first to use only rechargeable SCS pulse generators, the EVIDENCE study will provide up-to-date evidence on the treatment of failed back surgery syndrome.

Keywords: Clinical trial protocol, cost-effectiveness, failed back surgery syndrome, randomized controlled trial, re-operation, spinal cord stimulation

Conflict of Interest: Dr. North's current (Sinai Hospital of Baltimore) and former employers (Johns Hopkins University) received funding from industry (Boston Scientific, Inc.; Medtronic, Inc.; St. Jude Medical, Inc.) as does the non-profit Neuromodulation Foundation, of which he is an unpaid officer. He has consulting/equity interest in Algostim LLC. Dr. Kumar is a consultant to Medtronic, Inc., and has received funding for contributions to research papers and patient enrollment during the PROCESS study. He has no stock in Medtronic, Inc. He also is a consultant for Boston Scientific Corporation (BSC) but, to date, has received no funding and has no stock in BSC. Dr. Wallace is a consultant for BSC, has received honoraria for speaking for BSC, and has received research support from Medtronic, Inc. Dr. Henderson is a recipient of a Medtronic training and education grant; a scientific advisory board member with stock options for Nevro Corporation and for Intelect. Consultant with stock options for Proteus Biomedical; and a recipient of support from the John A. Burne, Davis Phinney, Keck, Coulter, and Michael J. Fox foundations and from the National Institutes of Health. Jane Shipley's employer (The Neuromodulation Foundation) has consulting agreements with and unrestricted educational grants from the companies that manufacture SCS equipment. Drs. Hernandez, Mekel-Bobrov, and Jaax are BSC employees and stockholders.

INTRODUCTION

This paper presents the protocol of the EVIDENCE study, the first multicenter multinational randomized controlled trial (RCT) assessing the therapeutic- and cost-effectiveness of spinal cord stimulation (SCS) versus re-operation in the treatment of failed back surgery syndrome (FBSS) and the first conducted with rechargeable implanted pulse generators (IPGs). Publishing protocols for comparative effectiveness research studies (1) documents the researchers' intentions in advance so that independent reviewers can verify the consistency of both trial execution and data analysis with the study protocol and protects against potential under-reporting of negative results (2,3).

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SCS has several advantages compared with re-operation: 1) a screening trial can predict the outcome of SCS, while no such trial is available to predict the outcome of re-operation; 2) SCS is designed to be reversible and adjustable, whereas the effects of re-operation are permanent; and 3) SCS is less invasive than re-operation. Despite these attributes, SCS is often reserved for patients who have failed multiple, and indeed all possible, re-operations—a strategy that might reduce a patient's chance of successful treatment with SCS.

To date, two RCTs have been reported on the use of SCS to treat FBSS: a single-center study comparing SCS with re-operation (4,5) and a multicenter study comparing SCS with conventional medical management (CMM) (6,7). In both studies, SCS proved to be superior to the alternative treatment. Nonetheless, in clinical practice, SCS is not yet offered to all appropriate patients.

Policy-makers rely on formal health technology assessments in order to make decisions that ultimately have a great impact on the accessibility of a medical therapy, such as SCS. In order to produce worthwhile recommendations, these assessments require up-to-date comparative effectiveness data derived from well-designed trials. Although evidence of comparative effectiveness is best provided by double-blind RCTs, it is not possible or ethical to conduct a blind trial of SCS because the technical goal of SCS treatment is to overlap the area of pain with perceptible paresthesia. We can, however, design unblinded RCTs that increase our confidence in the evidence that offers a basis for health care decisions about the use of SCS (8–10).

Additional evidence about the comparative effectiveness of SCS versus re-operation will influence the treatment of FBSS, which has a deleterious effect on a patient's quality of life and leads to continued, and often futile, consumption of health care resources.

METHODS

Study Design

Randomization to re-operation or SCS (1:1) is stratified by site and by each subject's number of prior lumbosacral surgical procedures (one versus multiple).

If a subject asks to receive the non-randomized treatment after undergoing the index procedure, this request will constitute "crossover" and signal failure of the randomized treatment. Crossover treatment can take place without a waiting period for any subject who fails an SCS screening trial or after the six-month post-index procedure visit for subjects undergoing re-operation or SCS implantation following a successful SCS screening trial. A disinterested third party will remind subjects of the crossover option at the six-month post-index procedure visit.

Enrollment in this multicenter RCT will be distributed competitively among a maximum of 40 sites in the USA, Canada, and Europe. Each study site must obtain Institutional Review Board approval of the protocol and written informed consent from all subjects. The protocol and consent forms are consistent with the International Conference on Harmonisation Guidance for Industry E6 Good Clinical Practice, the Declaration of Helsinki, and all local laws and regulations, as appropriate.

Patient Selection

Consecutive eligible patients at each study site are offered study participation. After subjects give informed consent to participation, they undergo additional (psychological and imaging) testing to confirm that they meet the selection criteria.

Subjects must be at least 18 years of age and have persistent or recurrent radicular neuropathic leg pain with concordant neurologic findings and surgically remediable pathology after one or more lumbosacral surgical procedures. They must have suffered this pain for at least six months at an intensity of 5–10 on a standard 0–10 numeric rating scale. The leg pain must exceed or equal any low back pain.

Eligible subjects must be candidates for both SCS and for a specific re-operation on the lumbosacral spine for persistent or residual root compression concordant with radicular pain. In each case, a second surgical opinion is obtained to confirm suitability of the specific re-operation proposed. An MRI or CT myelogram of the lumbar and thoracic spine (within 12 months) must rule out any pathology that might confound diagnosis and/or compromise SCS, and potential subjects must pass a routine (as for SCS) psychological/psychiatric evaluation, including substance abuse screening.

See Table 1 for subject exclusion criteria.

Data Collection

Baseline data are collected 0–60 days prior to the index procedure (the beginning of the SCS screening trial or the first study re-operation) and will include delineation of the area of FBSS-related pain.

A disinterested third party collects outcome data questionnaires at 3 months (90 $\pm$ 14 days), 6 months (180 $\pm$ 14 days), 12 months (365 $\pm$ 30 days), 24 months (730 $\pm$ 30 days), and 36 months (1095 $\pm$ 30 days) post-index procedure. Additional visits may occur at any time for the purpose of crossover, evaluation of adverse events, or routine SCS reprogramming.

Table 1. Patient Exclusion Criteria.

- Pain in a new distribution following the most recent lumbosacral surgical procedure
- Leg pain intensity consistently 10 on the 0–10 numeric rating scale during the past six months
- Presence of a disabling or potentially disabling neurologic deficit attributable to:
  - Surgically remediable root compression
  - Radiographic evidence of frank instability requiring fusion
  - Calcific arachnoiditis
  - Severe thoracic stenosis
  - Critical cauda equina compression
- A predominance of non-organic signs
- Occupational risk that would rule out SCS
- Local or systemic infection
- Medical or cardiac conditions, therapies, or diagnostic tests that preclude SCS and/or re-operation
- Factors that might interfere with accurate analysis of treatment effects, including:
  - Concurrent clinically significant or disabling chronic pain not attributable to FBSS
  - A significant dependency on prescription narcotic analgesics or benzodiazepines
  - Major untreated psychiatric comorbidity
  - Unresolved issues of secondary gain (such as pending litigation)
  - An expected inability to report treatment outcomes or operate the SCS system
- Pregnancy or planned pregnancy during the study period
- A life expectancy of less than three years
- History of a prior SCS procedure
- Presence of an intrathecal drug pump
- Participation in another clinical study that would confound data

An office visit is mandatory at 3, 6, and 24 months. At 12 and 36 months, subjects are encouraged to return to the clinic to complete data collection, but follow-up may be accomplished via mail or telephone.

For the purpose of follow-up pain assessments, subjects are asked to disregard any area of new pain that might have arisen during the study. (As is usual practice, however, subjects receiving SCS have programming adjustments as appropriate to treat any new pain, and any new pain will be recorded.)

Interventions

Subjects randomized to re-operation will undergo a surgical procedure to decompress involved neural structures with or without fusion and/or instrumentation.

Subjects randomized to SCS will undergo a minimum three-day screening trial, using one or two percutaneous electrodes or a surgically implanted paddle electrode. In the event that a paddle electrode is used for the screening trial or the implanted system, the only surgical procedure permitted is the laminectomy or laminotomy required to implant the electrode.

Upon completion of a successful screening trial, subjects are offered SCS implantation with the Precision® rechargeable SCS system (Boston Scientific Corporation, Valencia, CA, USA). Screening trial success is defined as subject report of ≥50% leg pain relief and satisfactory pain/paresthesia concordance or subject request for implantation and clinician concurrence. If the screening trial is initially unsuccessful, the clinician may extend or modify the trial, as appropriate.

During implantation of the SCS system, the clinician uses lead anchors and approved silicone elastomer adhesive to prevent electrode migration (11).

The time between the SCS screening trial and SCS implantation should not exceed 60 days, and the total time from baseline to SCS implantation should not exceed 90 days.

Adjunct Pain Treatment

All adjunct pain treatment is allowed except for non-study-related leg or back surgical procedures or intrathecal drug delivery.

Outcome Assessments

The co-primary endpoints are the proportion of subjects indicating ≥50% relief of leg pain without crossover to the other treatment at 6 and 24 months post-index procedure on a standard self-reported measure of percent pain relief.

The secondary endpoints include cost-effectiveness; relief of leg, back, and overall leg and back pain; change in disability and quality of life; and rate of crossover. We also are examining subject global impression of change, patient satisfaction with treatment, employment status, SCS pain/paresthesia overlap, and SCS programming data. Any device- or procedure-related adverse event and all serious adverse events (regardless of cause) will be reported and monitored by the adverse event committee. All serious adverse event reporting requirements will be met. The study schedule for the collection of outcome data is illustrated in Figure 1.

Sample Size

The study follows an adaptive design for sample size recalculation. The initial sample size of 132 subjects is based on an estimated proportion of subjects reporting ≥50% leg pain relief without crossover of 0.425 in the SCS group and 0.145 in the re-operation group, with a 10% attrition rate. Because of the relative scarcity of data on which to calculate our sample size, we will conduct an interim analysis to re-estimate these parameters after the first 20 subjects per group (40 subjects total) have reached 6 months post-index procedure. Based on the results of the interim analysis, the sample size may be adjusted to between 100 and 200 subjects, following predefined decision rules and the appropriate correction to preserve the overall Type I error of 5%. The initial per-site enrollment cap of 10 subjects also may be increased at this point, but when the overall study enrollment cap is reached, enrollment will cease regardless of whether individual sites have reached their per-site cap.

Statistical Hypotheses

The null hypotheses are that the proportions of subjects with ≥50% relief of leg pain from baseline without crossover at 6 and at 24 months post-index procedure are equal between the two randomized groups. The null hypotheses will be tested using a two-sided Fisher's exact test of equal independent binomial proportions. Because we will test each null hypothesis independently, we will employ Bonferroni correction for multiple testing in order to preserve an overall Type I error of 5%, with each of the two null hypotheses tested at a 2.5% significance level.

Analysis Populations

All primary and secondary endpoints will be analyzed at each time point on an intent-to-treat (as-randomized), modified intent-to-treat ("treated-as-intended," excluding subjects who crossed over prior to the analysis time point), and final-treatment basis.

Statistical Analyses

Statistical analyses will be performed using SAS System software, version 8 or later. An independent third-party statistician will validate all primary endpoint analyses.

Other Statistical Methods

After summarizing baseline data for each randomized group using descriptive statistics (e.g., mean, standard deviation, *N*, minimum, maximum) for continuous variables and frequency tables or proportions for discrete variables, we will calculate differences between treatment groups and their 95% confidence intervals and perform statistical testing as appropriate.

Clinical data across study sites as well as analyses over the stratification variable of one versus multiple previous lumbosacral surgical procedures will be pooled but also analyzed separately for each randomized group. Differences among study sites will be assessed to justify data pooling, using appropriate stratified and multivariate analysis techniques, including contingency tables, logistic regression for binary outcomes, and analysis of variance for continuous measures.

We will analyze follow-up data with appropriate univariate and multivariate techniques and illustrate time-to-event variables, such as crossover, with Kaplan–Meier plots. We will use the Cox proportional hazards regression model to assess the effects of risk factors on these variables.

Although we will analyze the data in modules based on study follow-up intervals, these analyses will not constitute formal

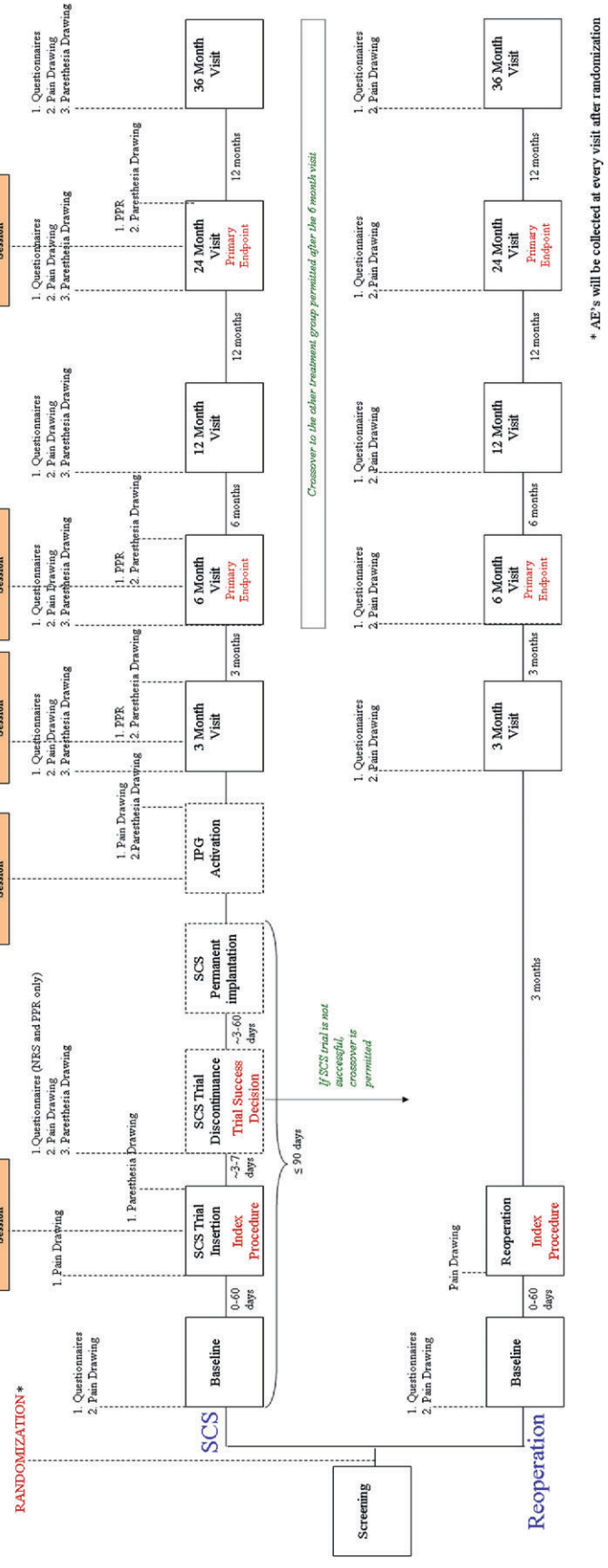

Figure 1. Study timeline. AE, adverse event; IPG, implanted pulse generator; NRS, numeric rating scale; PPR, percent pain relief; SCS, spinal cord stimulation.

interim analyses and will not affect the conduct of the trial or the final endpoint analysis; therefore, we will not adjust the alpha level.

Cost-Effectiveness Analysis

Analysis and reporting of the economic endpoints will follow recommended guidelines for cost-effectiveness analyses of data from RCTs (12–15). We will assess cost-effectiveness, defined as the ratio of the difference in arithmetic mean costs to the difference in arithmetic mean effects, at 6, 12, 24, and 36 months post-index procedure. The primary cost analysis will measure total direct medical costs, and the primary effect measure will be quality-adjusted-life-years. A secondary effect measure will be clinical success (≥50% leg pain relief without crossover). The analysis will include joint comparison of costs and effects and tests for stochastic uncertainty. Methods for projecting costs and effects beyond the trial period and results of this projection will be reported separately from the trial analysis (10).

We will calculate cost estimates by multiplying resource use per patient with unit-cost estimates derived from a variety of secondary data sources that will be detailed in a separate publication. Sources of unit-cost data will include publicly available fee schedules and manufacturers' estimated cost of equipment.

We will base the choice of costing method for the different countries represented in this trial on the availability of appropriate cost estimates. A fully pooled, multi-country cost analysis will be performed if feasible in order to maximize statistical power while maintaining the relationship among resource use, costs, and clinical outcomes (15–18).

We will provide descriptive statistics (mean, median, range, interquartile range) on resource data and overall costs for each assessment period and will report methods for addressing any missing data. We will transform variables as needed to conduct appropriate inferential statistics and will use statistical techniques, such as Box-Cox analysis or non-parametric bootstrapping, to determine the cost transformation that best fits the data in order to compare arithmetic mean costs and calculate confidence intervals.

We will examine the sensitivity of cost estimates to other variables using probabilistic simulation and the most advanced modeling techniques.

Quality-Adjusted-Life-Years

We will estimate quality-adjusted-life-years for each subject by multiplying each subject's utility score by the time spent in a specific health state and will test group differences at each follow-up point using analysis of covariance (adjusting for baseline values). We will measure quality of life during any adverse event.

DISCUSSION

The rationale for the multicenter multinational design of the EVIDENCE study is to expand upon the results obtained through the single-center RCT (4) by incorporating a larger sample size and multiple study sites. The EVIDENCE study also will update the single-center results by incorporating improvements in SCS techniques (11) and equipment (e.g., rechargeable IPGs) as well as in re-operation techniques.

The scientific literature on SCS has been reviewed critically, and recommendations have been made for the conduct of SCS studies (10). Such recommendations are easier to make than to follow (19,20); commentators call for RCTs (10) but in practice conduct non-randomized studies with questionable comparison groups and methodology (20). In accord with recommendations calling for RCTs with a priori sample size power calculations; planned follow-ups at regular intervals; and use of valid, reliable measures, the EVIDENCE study incorporates the most rigorous and rational evidence-based clinical study practices possible.

Consistent with the protocols of the previous RCTs and with its sponsorship, the EVIDENCE study requires use of SCS equipment designed by a single manufacturer (in this case, Boston Scientific Corporation of Valencia, CA, USA). Some commentators note that industry-funded studies are more likely than others to produce results favorable to the sponsor (21). Multiple measures taken to ensure research integrity in the EVIDENCE study include a strict randomization procedure, the use of an impartial third party to collect data, the use of an independent group of statisticians to analyze data, and the execution of the study in multiple settings by multiple clinicians.

The EVIDENCE study protocol has been designed to optimize the care that study subjects receive and to protect patient safety. SCS is a minimally invasive reversible therapy, and technological advances have made implantation progressively easier. Thus, more and more clinicians are performing SCS. Offering SCS to the correct patient, using appropriate equipment, and correct techniques requires careful deliberation and adequate implanter experience. The results of this study may be generalized to the extent that SCS practitioners employ appropriate patient selection criteria and equipment as well as appropriate screening trial and implantation techniques. We detail these methods here sufficiently that others may replicate our results in the "real world delivery of health care" (19,20).

As did both previous RCTs (4,6), the EVIDENCE study excludes patients with more than 50% back pain. Back pain might have a significant nociceptive component, and SCS is used to treat neuropathic pain. Back pain is the only comorbid pain condition allowed, and we considered it best to avoid emphasizing a potentially confounding source of pain. Following normal clinical practice, however, the EVIDENCE study requires adjustment of SCS parameters to maximize pain/paresthesia overlap; furthermore, back pain and paresthesia coverage data will be collected and analyzed.

Patient enrollment was facilitated in the single-center RCT (4) because contemporary practice called for a patient to undergo every possible indicated re-operation before SCS. Thus, SCS was not yet available to eligible patients outside of the study, but patients who enrolled had a 50% chance of an SCS screening trial at an earlier than usual stage of treatment. The results of the single-center RCT made it clear, however, that withholding SCS until all re-operations had failed was not necessary. This means that patients who are eligible for enrolling in the EVIDENCE study have both SCS and re-operation available without study participation.

In the single-center RCT (4), SCS was both less expensive than re-operation and economically dominant in terms of cost-effectiveness and cost utility (5). The EVIDENCE study's full economic evaluation will update these results by reflecting current medical resource use and costs. The EVIDENCE study's 36-month follow-up will be longer than that of both previous RCTs (4,6); nevertheless, even this extended time period will likely not reflect the full impact on cost-effectiveness of the use of a rechargeable IPG.

CONCLUSION

The EVIDENCE study will add valuable and up-to-date evidence on the therapeutic-effectiveness and cost-effectiveness of SCS versus re-operation in appropriately selected patients with FBSS. Study site certification and patient enrollment are ongoing.

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Authorship Statements

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COMMENTS

This is a publication of a protocol, I hear you opine. Yes it is and there is a very good reason. Neuromodulation science is bedeviled with case series reporting. This is bound to happen in a relatively young and rapidly progressing field. However we cannot go along like this forever. We have to have the real science that provides the evidence base if we are going to break into mainstream clinical practice and improve the quality of life for a much larger group of patients. This journal and the International Neuromodulation Society support this endeavour. It is landmark research such as this that actually leads to a step change. The need is insatiable. My dream is that every patient who has such a neuromodulation device should simultaneously be enrolled in a research project both randomised and comparative or investigational or even as a registry. Thanks to these authors we will have yet another high quality RCT to support the evidence for what we are all trying to do. It is right that this too rare intention to produce high quality science is included in our journal. As a society we should insist that they publish their results in our journal too.

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North and coworkers report their proposed study design for a multicenter prospective, randomized controlled trial of spinal cord stimulation versus spinal reoperation in patients with failed back syndrome. Dr. North published several years ago a single center prospective randomized controlled trial which demonstrated both increased efficacy and cost effectiveness of SCS as compared to reoperation. The time is ripe for replication of this study using more modern technology and using a multicenter design. The study is carefully considered, well designed and we hope for rapid patient accrual and to the results of the trial.

One might well ask why publish a proposed trial in Neuromodulation and instead insist on publication of the completed trial and its results. This argument is cogent and certainly has merit, but I believe that there are other goals that early publication and review serve for the neuromodulation community. First, subjecting such studies to rigorous external review prior to the initiation of the study can only enrich the final results and limit the need for late study revision or posthoc data analysis both of which are inappropriate. The resources available to run such large scale multicenter trials are significantly limited and as a field we need to ensure that they are used wisely.

Secondly, the paper by North and coworkers not only presents the study protocol but also discusses the complex considerations that led to the final research protocol. These issues are those that all neuromodulation researchers must face when designing studies and presenting them to our institutional review boards or the FDA. We all benefit from reviewing the careful deliberations by experienced neuromodulation researchers when we then attempt to design or critique other studies.

Finally, the field of neuromodulation, patients and third party payers have long demanded Class I data to support the use of neuromodulation therapies. We have the obligation to ensure that these studies are well designed, executed and reported. By making members of the neuromodulation community aware of such studies as they are initiated, we can help to provide subject referrals to assist with patient accrual and the timely completion of the study and provide a potential therapeutic option for our patients who might not otherwise have access to these therapies.

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Comments not included in the Early View version of this paper.

