Received: September 16, 2020 Revised: January 11, 2021 Accepted: February 9, 2021

(onlinelibrary.wiley.com) DOI: 10.1111/ner.13381

Clinical Trial Designs for Neuromodulation in Chronic Spinal Cord Injury Using Epidural Stimulation

Maxwell Boakye, MD, MPH, MBA[1,2]; Beatrice Ugiliweneza, PhD, MSPH[1,2,3]; Fabian Madrigal, MD[1]; Samineh Mesbah, PhD[2]; Alexander Ovechkin, MD, PhD[1,2]; Claudia Angeli, PhD[2,4,5]; Ona Bloom, PhD[6,7,8,9]; Jill W. Wecht, EdD[9,10]; Bonnie Ditterline, PhD[1,2]; Noam Y. Harel, MD, PhD[9,10]; Steven Kirshblum, MD[11,12]; Gail Forrest, PhD[12,13]; Samuel Wu, PhD[14]; Susan Harkema, PhD[1,2,5]; James Guest, MD, PhD[15]

ABSTRACT

Study Design: This is a narrative review focused on specific challenges related to adequate controls that arise in neuromodulation clinical trials involving perceptible stimulation and physiological effects of stimulation activation.

Objectives: 1) To present the strengths and limitations of available clinical trial research designs for the testing of epidural stimulation to improve recovery after spinal cord injury. 2) To describe how studies can control for the placebo effects that arise due to surgical implantation, the physical presence of the battery, generator, control interfaces, and rehabilitative activity aimed to promote use-dependent plasticity. 3) To mitigate Hawthorne effects that may occur in clinical trials with intensive supervised participation, including rehabilitation.

Materials and Methods: Focused literature review of neuromodulation clinical trials with integration to the specific context of epidural stimulation for persons with chronic spinal cord injury.

Conclusions: Standard of care control groups fail to control for the multiple effects of knowledge of having undergone surgical procedures, having implanted stimulation systems, and being observed in a clinical trial. The irreducible effects that have been identified as "placebo" require sham controls or comparison groups in which both are implanted with potentially active devices and undergo similar rehabilitative training.

Keywords: Neuromodulation, clinical trial, epidural stimulation, spinal cord injury, rehabilitation

Conflict of Interest: The authors have no conflicts of interest or financial disclosures.

Address correspondence to: Maxwell Boakye, MD, MPH, MBA, FACS, Department of Neurosurgery, University of Louisville, School of Medicine, 220 Abraham Flexner Way, Louisville, KY, USA. Email: max.boakye@louisville.edu

[1] Department of Neurological Surgery, University of Louisville, Louisville, KY, USA;
[2] Kentucky Spinal Cord Injury Research Center, University of Louisville, Louisville, KY, USA;
[3] Department of Health Management and Systems Sciences, University of Louisville, Louisville, KY, USA;
[4] Department of Bioengineering, University of Louisville, Louisville, KY, USA;
[5] Frazier Rehabilitation Institute, University of Louisville Health, Louisville, KY, USA;
[6] Feinstein Institute for Medical Research, Manhasset, NY, USA;
[7] Department of Molecular Medicine, Zucker School of Medicine at Hofstra Northwell, Manhasset, NY, USA;
[8] Department of Physical Medicine and Rehabilitation, Zucker School of Medicine at Hofstra Northwell, Manhasset, NY, USA;
[9] James J Peters VA Medical Center, Bronx, NY, USA;
[10] The Icahn School of Medicine at Mount Sinai, New York, NY, USA;
[11] Kessler Institute for Rehabilitation, Department of Physical Medicine and Rehabilitation, Rutgers New Jersey Medical School, Newark, NY, USA;
[12] Human Performance and Engineering Research, Kessler Foundation, West Orange, NJ, USA;
[13] Department of Physical Medicine and Rehabilitation, Rutgers New Jersey Medical School, Newark, NJ, USA;
[14] Department of Biostatistics, CTSI Data Coordinating Center, University of Florida, Gainesville, FL, USA; and
[15] Neurological Surgery, and the Miami Project to Cure Paralysis, Miller School of Medicine, Miami, FL, USA

Source(s) of financial support: None.

INTRODUCTION

Spinal cord injury (SCI) affects individuals profoundly, with an estimated prevalence in the United States of up to 368,000 people (1,2). Living with SCI is difficult, expensive, and fraught with the evolution of secondary health problems. Autonomic and homeostatic derangements are major secondary problems after chronic SCI, for which there is currently limited therapy (3–5). Lifetime healthcare and living costs for an individual injured at age 25 are estimated to range from $1.7 million to greater than $5 million (1). Recently, neuromodulation technologies, spinal cord epidural stimulation (scES), have shown promise as a neurorestorative therapy for chronic SCI in open-label studies. The reported effects include the recovery of voluntary movement (6–11), walking/stepping (9,12,13), improved cardiovascular regulation (10,14–17), and improvement in other physiological consequences of SCI (18,19).

At the University of Louisville, the application of scES to SCI is an experimental procedure that currently involves surgical implantation of an electrode array over the spinal cord dorsal L1-S1 segments. The neurostimulator device was initially developed to treat intractable pain, and such systems have been used in thousands of patients worldwide, with low rates of serious complications (20–25). Further, we have developed enhanced surgical safety protocols for scES in individuals with SCI (26). In these individuals, the lumbosacral device location enables activation of motor and autonomic networks, depending on the parameters and patterns of electrode activation selected.

Individuals with SCI report that they are aware when the stimulation is on, complicating attempts to blind the effects of scES during mapping, training, and assessment studies. For motor activities such as standing, voluntary movement, or locomotion, participants also report increased ''awareness'' and connection to previously paralyzed body regions during stimulation. Some individuals describe this as a change in sensation and/or cognizance of the paralyzed region's position. When the stimulation pattern is focused on regulating cardiovascular function, the changes in heart rate and blood pressure are also readily perceived by the individual, who report feelings of increased vitality. Thus, given the typical scES settings that have succeeded in improving functions, participant awareness during stimulation appears to be unavoidable, limiting the potential for double-blind trial designs. While there can be instantaneous effects of scES in chronic SCI, such as the ability to move a previously paralyzed joint or blood pressure stabilization, benefits observed have been cumulative in most reports (27).

In recognizing the need for more clinical research on neuromodulation in SCI, an NIH consortium of leaders in the field concluded that ''*there is a high level of enthusiasm for developing the potential of epidural stimulation as an intervention for people with SCI*'' (28). To date, the research studies of scES for SCI have been reported in small numbers of participants, in uncontrolled single-institution trials (6,8–10,13–15,17–19,29). According to the current understanding of the stages of the research continuum (30), investigations to-date have been in the early clinical testing translation 1 (T1) phase (30,31), defined as ''*the transition from basic science to early clinical trial phases*.'' The subsequent T2 research Phase encompasses the establishment of the effectiveness of an intervention and progress toward clinical guidelines for its use. To achieve the evidence basis required by stakeholders to support clinical adoption of scES for SCI, we should understand errors of the past. The design of the T2 research studies requires careful consideration. In particular, the demonstration of efficacy requires adequate control groups to determine the specific contribution of the electrical stimulation pattern provided by the device as compared to the effects of trial participation, surgical implantation, and the rehabilitation component of the study. In this manner, we determine the evidence basis for clinical implementation through well-planned prospective studies and critical review of current evidence. Further, a rigorous examination of safety (both short term and long term) is required beyond anecdotal reports. The safety evidence is especially critical to inform a potential expansion of subject enrollment of those with less severe neurological injuries.

In studies of implanted spinal and cranial neuromodulation devices for pain, tremor, depression, and other indications, it has been a convention to call nonspecific effects that may be beneficial ''the placebo response.'' We recognize that this is a complex concept in the context of the neurorehabilitative setting of scES for chronic SCI. Here, we use ''placebo'' to indicate those effects that do not directly arise from the configured electrical stimulation.

In the pivotal confirmatory phase for new therapies, a recognized standard for clinical trial design is a prospective, randomized, placebo-controlled, double-blinded, multisite clinical trial, where possible. However, due to unique aspects of neuromodulation, specific problems in the adequate control of such pivotal studies require careful consideration. These include that scES requires initial surgical implantation that may be associated with placebo effects and difficulties with blinding. Therefore, the designs for such T2 studies should incorporate methods that are effective in controlling for potential biases due to the spectrum of effects besides those of the targeted stimulation. Fortunately, we can learn from prior studies that developed the evidence basis for epidural stimulation for pain and deep brain stimulation (DBS) for Parkinson's tremor (32) in which these potential biases were encountered. Further, gene therapy and tissue and cell transplant studies in Parkinson's conclusively revealed the critical importance of sham controls (33–35). It is important to also point out that unlike trials for pain or DBS, scES studies for SCI often involve neurorehabilitation that is likely contributory to progressive stimulation benefits.

The purpose of this article is to inform scES neurorestoration research designs and propose options regarding optimal and feasible designs to generate clinical evidence while minimizing bias. We thus review clinical trial designs that have been utilized with other neuromodulatory technologies requiring surgical implantation that involve electrical stimulation of neural tissue to restore function, including DBS and studies of scES for back and anginal pain. In addition, we reviewed DBS for depression and obsessive–compulsive disorder, where placebo effects are prominent. We then incorporate these trial designs with a discussion informed by a decade of experiential knowledge of scES studies in chronic SCI. For this review, we define a clinical trial according to the current NIH definition, ''A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes'' (36).

For drug studies, randomized, double-blind, and placebo-controlled trial designs, as well as meta-analyses of such studies, have provided evidence to guide clinical practice (37). Randomization helps to control selection bias, balances groups on observed and unobserved characteristics, and is an optimal study design to

support causal inferences (38–41). Blinding of patients and study personnel may help to reduce bias and overestimation of treatment effects, although there remains some controversy in this area (42–44). Comparison to placebo helps to control for nonspecific effects, which can be problematic in surgical trials (45). Patients undergoing surgeries as a clinical trial component may experience effects related to device implantation surgery, anesthesia, complications, and increased medical attention. In a recent systematic review of spinal surgery studies, 39 out of the 53 trials that were examined showed improvement in the placebo arm (46).

In the context of nondrug interventions like scES, the term ''sham'' refers to a control in which the therapeutic intervention is mimicked but omits an essential therapeutic element to create the uncertainty needed to reduce bias in the study.

> A sham procedure can be defined as one performed on a control group participant to ensure that he or she experiences the same incidental effects of the operation or procedure as do those participants on whom a true operation is performed (47).

There are several important examples of surgical procedures for various indications, whose initial reports were promising but later failed to demonstrate superiority when appropriate sham-controlled trials were performed (48,49). Notable examples were studies of fetal tissue and cell transplantations in the brain for Parkinson's disease. At one point in time, these procedures seemed a successful treatment for Parkinson's. However, the magnitude of the placebo effect may increase as the invasive aspects under investigation are increased (50,51). After significant debate over the ethics of exposing patients to sham surgery, subsequent sham-controlled studies of tissue and cell transplantation in Parkinson's showed no meaningful difference between transplanted and sham groups. Further, the sham control group also made it possible for the field to learn of serious off-target effects related to the grafts (52,53). However, in clinical trials involving neuromodulation surgical procedures, it may be difficult to devise a reasonable sham. In addition to surgical placebo effects, one needs adequate controls for the electrical stimulation itself. The US Food and Drug Administration (FDA) recognizes that in some trials, sham blinding is not feasible (3).

DESIGN CHALLENGES FOR MEDICAL DEVICE TRIALS

The effect size is a central consideration in neuromodulation studies where large effects make discernment of efficacy easier. However, the effect is a composite of multiple factors not only the stimulation. Furthermore, the precise mechanisms of action in the application of stimulation paradigms to target outcomes such as functional autonomic restoration or standing and walking are still under investigation and incompletely understood. This makes it more difficult to create sham paradigms to create the perception of stimulation that do not influence the target outcome. Further, to investigate for the linkage between stimulation configurations, the context of application, and measured effects, it is especially important to carefully specify stimulation configurations individually.

Control groups for medical device trials have included optimal ''standard'' care, fully implanted inactive devices, and perceptible sham stimulation that is not optimized for the target outcome with varying degrees of potential blinding. Currently, trials of high-frequency stimulation for pain that is not perceptible to the participant subject are making the design of scES pain studies simpler (54), yet continue to reveal large placebo effects (55). However, this imperceptible stimulation modality is not effective for the SCI endpoints under current evaluation, such as improved motor or autonomic function.

Most neuromodulation studies are designed to recruit a cohort of participants and conduct testing in parallel over time. In a parallel open-label trial, the active implant is compared with optimal medical therapy (Fig. 1a). This design was initially useful in evaluating DBS for Parkinson's disease, where DBS plus optimal medical therapy was compared to optimal medical treatment alone (56). Such controls, however, do not determine the DBS device-specific placebo effect, which may be considerable (57). Furthermore, concerning chronic SCI, there is continuing controversy regarding the optimal pharmacological or medical treatment for managing medical consequences, for example, blood pressure fluctuations and spasticity, that limit the standard-of-care control group options for SCI neuromodulation studies. Given these challenges around a conclusive demonstration of efficacy, SCI device trials should control for the known potential effects considered as ''placebo.'' These are illustrated in Fig. 1 to include surgical implant surgery effects, Hawthorne observer effects.

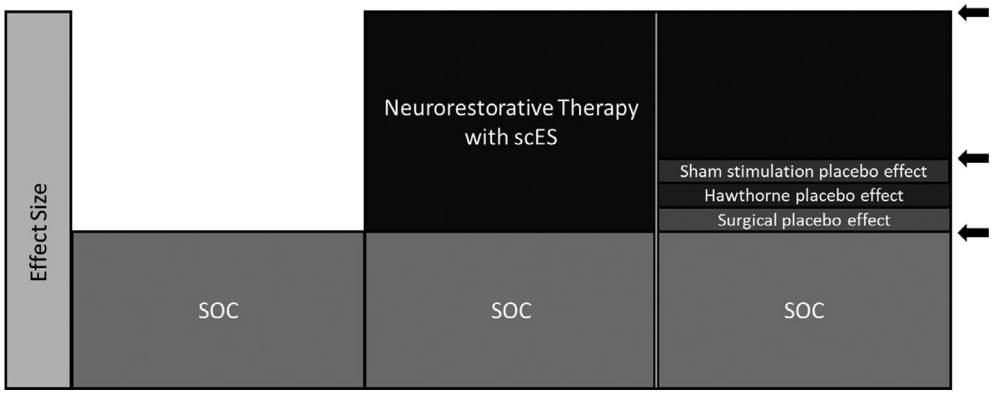

Figure 1. Visual representation of the impact of various forms of placebo as a component of an observed therapeutic endpoints. Here SOC would be the treatment effect in the absence of scES neurorestorative therapy. In the middle panel is illustrated an overall effect size, and in the left panel the proportions of the observed effect that may derive from placebo effects (black arrows).

Table 1. Advantage and Disadvantage of Clinical Trial Designs.

Design	Advantages	Disadvantages
Parallel open label	No carryover or period effects	Hawthorne and placebo effects present. Unblinded
Parallel implant, silent implant control	Silent implant controls for surgical placebo effects	Exposes subjects to surgical risks without any intentional treatment benefits
Parallel implant, sham stimulation control	Sham controls for all types of placebo effects	Sham more likely to have off-target effects, either beneficial and/or adverse
Single crossover	Crossover to active implant allows all participants a chance to gain the potential benefits. Increases the sample size for the safety assessment of the active stimulation	Without active to inactive crossover, unable to determine the permanence of effects
Double crossover	Balanced crossing allows the within-participant comparison of all interventions	Optimal washout period may be unknown or even non-existent. Participants in active therapy may be reluctant to switch

Optimally controlled studies also include a third level of control—an intervention arm that effectively mimics the implanted device in a nontherapeutic but active mode—(sham or ineffective stimulation).

Given the inherent risks of surgery, assigning individuals to a non-therapeutic surgically implanted device in a parallel-arm study raises ethical concerns if there is no intended benefit to the enrolled participant. For these reasons, crossover designs have gained favor in device trials. Potential longitudinal research designs include parallel open-label, parallel implant, single crossover, and double crossover designs (58). The advantages and disadvantages of these designs are described in Table 1, and schematic representations are described in Fig. 2. In the parallel open-label trial, the active implant is compared with optimum medical therapy (Fig. 2a). A second version of the parallel implant design compares an active implant to an identical electrically inactive (silent) implant as the control group (Fig. 2b). More optimal is the parallel design in which the implant delivers an ineffective but active (sham) stimulation (Fig. 2c). In this scenario, both groups undergo stimulation during the same study period, except that the stimulation in one group is not targeted to influence the primary outcome. In the single crossover design (Fig. 2d), there are randomized treatment and sham (ineffective) stimulation control groups, similar to the parallel implant design, except that the sham stimulation is eventually switched to effective stimulation during the trial after the crossover time point and a washout period. The double crossover design involves the crossover of each group to the other group/condition after a specified period of time (Fig. 2e). The option of the crossover also increases the sample size for monitoring safety of the active stimulation. Two other suggested scES trial designs are further described below. It should be emphasized that in the context of neuromodulation for restoration after SCI, all experimental and control groups undergo an equal amount of neurorehabilitation, which is essential to the success of scES.

Other aspects of stimulation, such as evidence of battery utilization and need for recharge, can also influence blinding. In scES studies for neuropathic pain, eight high-quality studies were identified in a recent systematic review (59). All used a randomized, double-blinded crossover design (Table 2) comparing one or more active paresthesia paradigms with silent (55,63), "placebo" (60–62,64,67), or active control (65). Silent control, in which no stimulation was delivered, was defined as a "*control where all study procedures were equal between arms including implantable pulse generator (IPG) linked behaviors* (*i.e., need for recharging*)." In one study (55), the silent control was described as "*the generator turned on and discharging, but without electricity transmitted to the lead*." In the second study (63), the stimulator was turned off after the completion of identical programming to the active intervention and after the current leak programming. Placebo was defined as a "*control where the IPG was inactive, and at least one of the study procedures was different between the arms* (*i.e., no IPG spontaneous discharge, i.e., built-in current leak*), *admitting overtly the possibility of unblinding*." In another study, low-amplitude burst stimulation was used as an active control (65). The designs used in these studies had a number of problems illustrating the difficulties of performing a rigorous well designed and controlled scES trial. Four of the eight studies did not have a washout period between crossover phases (55,60,64,66). Six studies had active tonic stimulation before randomization, and only two studies included patients without prior stimulation (61–66). Two studies evaluated the effects of the order of stimulation (55,63). Table 2 also shows the benefits of including sham or placebo controls, as in many of the studies, active stimulation was no better than the sham or placebo (55,60,62–64). Details of the randomization and concealment were missing in four studies (60,62,65,66).

The two largest clinical trials of DBS for depression (57,68) utilized a randomized, double-blind, parallel design with a silent implant control (Table 3) (70). In a third large trial, an open-label phase was followed by a randomized, double crossover phase using a silent implant control (69). In DBS studies, the silent implants showed a treatment effect in about 17% of participants (57), which may be attributed to micro-lesional effects from the implant (71–73). This demonstrates that even the use of a silent implant alone may not control for the effects of implantation. For brain implants, in addition to the placebo effects of surgery, several additional effects can occur as a result of implantation within tissue and circuit-level effects. The target circuits are complex, and the induced currents are never entirely or solely directed to the targets. Further, as with the spinal cord, mechanisms of action are not fully understood.

ETHICAL CONSIDERATIONS FOR SHAM CONTROL GROUPS

The ethical implications of sham surgical controls were extensively reviewed and summarized in a Yale Law and Policy Review article in 2016 (74). The ethical considerations of research include societal as well as individual benefits. An objection to sham

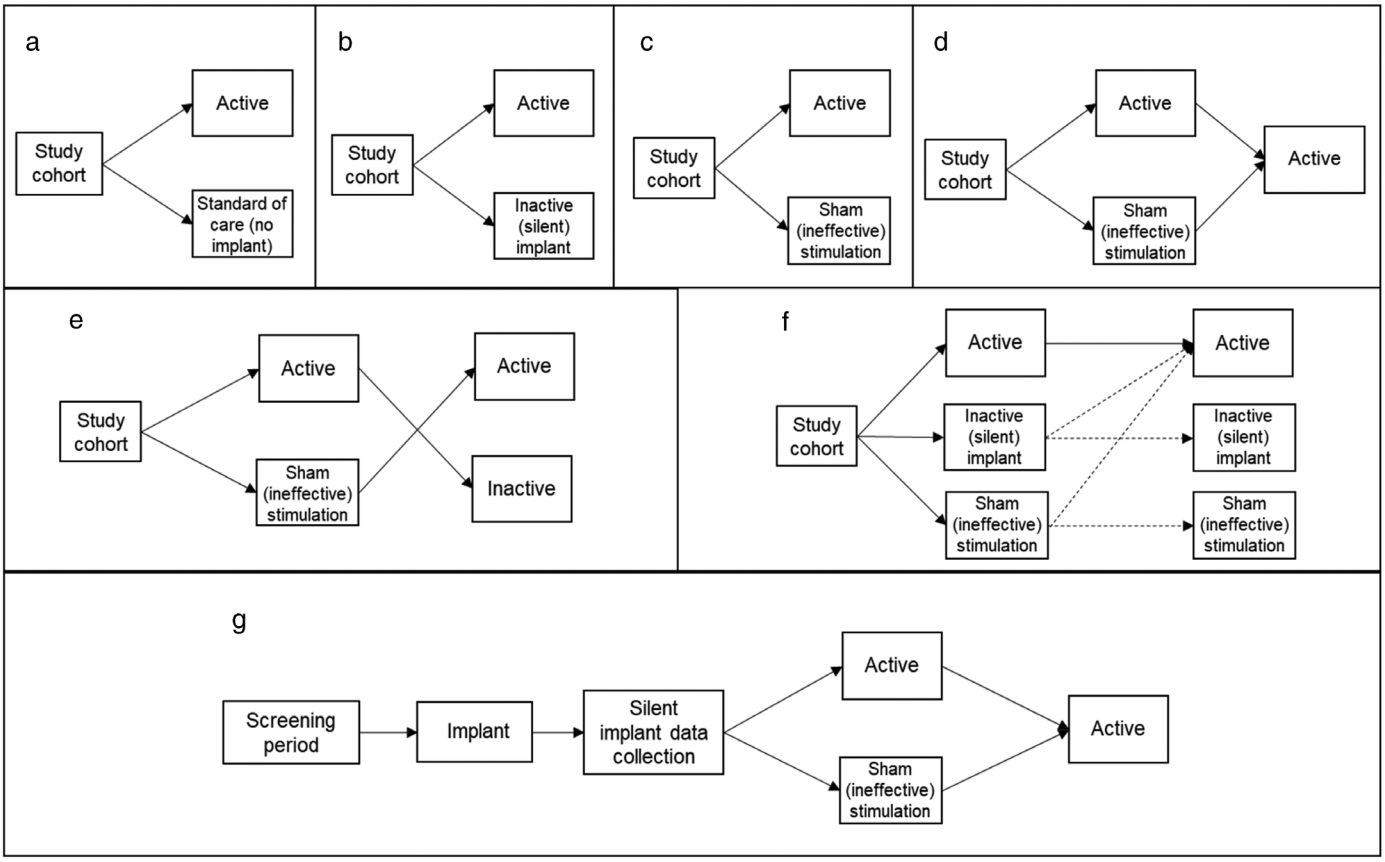

Figure 2. Potential clinical designs for randomized clinical trials using scES. (a) Open-label design using standard of care or optimal medical therapy as control. (b) Parallel Implant design with inactive (silent) implant controls. (c) Parallel implant design with sham (ineffective) stimulation controls. (d) Single crossover design with sham (ineffective) stimulation controls. (e) double crossover design with sham (ineffective) stimulation controls. (f) Three-arm design using both silent (inactive) implant and sham (ineffective) stimulation control groups, and converting the inactive implants and/or the sham stimulation to active/targeted stimulation after the crossover point. (g) Proposed study design for testing effects of scES in SCI. All subjects are implanted and undergo similar data collection during a post-surgical silent implant period prior to randomization to an initial active or sham (ineffective) stimulation period followed by crossover of sham stimulation to effective (targeted) stimulation to increase the acquisition of safety data.

procedures is that they may impose greater than minimal risk to study subjects with no corresponding direct benefit. Thus, a sham may create an imbalance of benefit between society and the individual trial participants that is inherent to a situation of equipoise (75).

Spinal epidural stimulators are now classified as Class II medical devices (21CFR882.5880). They were reclassified from Class III "high risk" in 2000 after substantial safety data had accrued, and the specific risks were known more fully. This decision has been challenged by reports that implanted SCS devices are not safe enough to warrant the lower classification (76). Concerns have also been raised regarding an inadequate burden of proof regarding efficacy in some regulatory pathways (77). Some devices were approved in other jurisdictions based on inadequately controlled studies and were subsequently found to have no benefit when tested in sham-controlled studies (78,79). Sham and inactive control groups are deemed very important where there is equipoise regarding a therapy or when the surgical invasivity can be minimized or is inherently less risky than, for example, a brain tissue transplant. Different ethical norms apply when the roles of clinicians are shifted toward acting with impartiality as scientists.

Methods to mitigate the risk of invalid surgical trials include rigorous study designs, careful, informed consent with full disclosure regarding sham and inactive assignments, investigators with established surgical skills, no medical charges to participants for the device or trial participation, and no industry-related conflicts-of-interest among the investigators. In addition, for implanted neuromodulation trials, the full spectrum of beneficial and/or adverse effects may take several years to become evident, for example, speech problems associated with thalamic DBS (80). Regarding the ethics of sham-controlled studies, it was concluded that where possible, all subjects should be implanted with functional devices, even if they are initially inactive, within a trial design that provides beneficence.

THE DESIGN OF scES TRIALS IN CHRONIC SCI

Due to the process of enrollment and randomization, expectations around surgical implantation, and the need for individualized testing and optimizing of scES parameters to the target outcome, several placebo and confounding effects may arise in scES device SCI studies. First, the surgical procedures for scES implantation involve up to five hours of general anesthesia, muscle dissection, bone removal, and leave notable incisions. Second, scES creates paresthesias that are difficult to blind in individuals assigned to active stimulation or to mimic in individuals assigned to inactive/silent implants. Third, implanted devices can indirectly

Table 2. Study Designs in Randomized Double Blinded Clinical Trials of scES for Pain.

Author	Groups	Critique
Al-Kaisy et al. (55)	Twenty-four patients compared 1200 Hz, 3030 Hz, or 5882 Hz active stimulation(stim) vs. sham (IPG turned on and discharging, but without electricity transmitted to the lead)- Design: Double blinded multiple crossover with four phases of three weeks duration each Outcome: Visual analog pain scores (VAS) Results: 5882 Hz stimulation provided more pain relief than sham stimulation	Washout period: none Prerandomization stimulation: no Assessments between phases: yes, but they used only data from baseline and last three days of trial for analysis Sham/Placebo effect: 63% of patients were either very satisfied or somewhat satisfied with the sham treatment. Sham was not significantly different from stimulation at 1200 Hz and 3030 Hz
De Ridder et al. (60)	Fifteen patients-tonic vs. burst stim vs. placebo Design: Double blinded multiple crossover, three phases of one week duration each Primary outcome: VAS Results: Burst stim was superior to sham	Washout period: none Prerandomization stimulation: yes Assessment between phases: yes Sham/Placebo effect: tonic stimulation not superior to placebo stimulation for pain suppression
Kriek et al. (61)	29 patients 40, 500, 1200 Hz, burst stim vs. placebo (device off after paresthesias). Double blinded multiple crossover Outcome: VAS Results: Significant pain reduction with all active stim compared with placebo stimulation	Washout period: two days Prerandomization stimulation: yes Assessment between phases: yes Sham/Placebo effect: all stimulations were superior to placebo stimulation although Placebo had small effect—VAS decreased from 7.3 to 6.3
Meier et al. (62)	Fourteen patients stim vs. placebo (device off) Design: double blinded double crossover two phases Outcome: quantitative sensory testing Results: thermal and mechanical thresholds and pain were similar during Stim and placebo	Washout period: 10–12 hours Prerandomization stimulation: yes-tonic of two weeks duration Assessment between phases: yes Sham/Placebo effect: no difference in primary outcome
Perruchoud et al. (63)	Thirty-three patients—high-frequency stim vs. sham (device off after programming) Design: Double blinded multiple crossover four phases of two weeks duration each Outcome: Patient's global impression of change (PGIC) Results: HFSCS was equivalent to sham for the primary outcome	Washout period: conventional stim Prerandomization stimulation: yes-tonic of two weeks duration Assessment between phases: yes Sham/Placebo effect: HFSCS was equivalent to sham
Schu et al. (64)	Twenty patients-tonic stim, burst stim, vs. placebo (device off) Design: Double blinded multiple crossover six phases of one-week duration each Outcome: Numerical rating scale (NRS) Result: Burst stim significantly better than placebo	Washout period: none Prerandomization stimulation: yes-tonic of at least six months duration Assessment between phases: yes Sham/Placebo effect: mean NRS score was not significantly different between 500-Hz tonic stimulation and placebo stimulation
Tjepkema-Cloostermans (65)	Forty patients—high amplitude burst vs. low amplitude burst vs. tonic stim Design: Double blinded double crossover, three phases of two weeks duration Primary outcome: VAS Results: VAS was lower for high and low amplitude burst stimulation compared with tonic stim	Washout period: two weeks of tonic stimulation Prerandomization stimulation: yes-tonic of at least six months duration Assessment between phases: yes Sham/Placebo effect: No sham or placebo
Wolter et al. (66)	Ten patients—suprathreshold vs. subthreshold stim vs. no stimulation Design: Double blinded double crossover two phases of one-week duration each Outcome: NRS Results: suprathreshold was significantly better than subthreshold and no stim Subthreshold was better than no stim	Washout period: none Prerandomization stimulation: yes-tonic of at least four weeks duration Assessment between phases: no Sham/Placebo effect: both suprathreshold and subthreshold was statistically better than no stim

modulate the entire nervous system and may rarely cause euphoria or other mood-altering effects. Fourth, even if a technology existed to create a ''perfect sham'' that incorporates paresthesias, it is considered unethical to surgically place a sham scES device that ultimately has no potential for benefit to the participant. Given the existing FDA approvals for neurostimulation devices,

Table 3. Randomized Clinical Trials of Deep Brain Stimulation for Depression.

Author	Groups	Design	Outcome	Critique
Bergfeld et al. (69)	Twenty-five patients—with treatment resistant depression (TRD) open-label followed by active stim vs. sham (device off)	Bilateral implants to the nucleus accumbens Open-label optimization followed by double-blinded sham-controlled double crossover of 12 weeks duration followed by another open-label phase	Three depression rating scales of which Hamilton depression rating scale was the primary measure A patient with 50% score reduction was considered to be responder (8/25) ITT	The sham phase is not reported and the overall study was inconclusive although an effect was maintained in responders The complexity of severe depression complicated the study due to drop-outs and cross-overs deemed to be unsafe
Dougherty et al. (68)	Thirty patients with TRD Active stim vs. sham (device off)	Baseline open label phase followed by double-blinded parallel design followed by an open-label period and continuation open label phase with long term follow-up to three years	Montgomery–Åsberg Depression Rating Scale, with a responder defined as a 50% reduction No difference in the response rates between the active and control groups was seen	Bipolar stimulation was used during sham phase so that notable paresthesias were not produced in either group. The blind was confirmed by asking subjects if they thought were on or off and confirmed to be valid. The study was initially powered for 208 subjects 90% power, 0.025 significance. The study stopped enrollment after the first 30 subjects (interim analysis) and thus the comparisons are not statistically valid to confirm or disprove the null hypothesis. While the efficacy of the DBS to treat TRD was not established, the sham was an effective treatment arm concealment It is further notable that all subjects showed a decrease in depression during the study indicating a placebo effect for the DBS implant
Holtzheimer et al. (57)	Ninety patients with TRD Active stim vs., sham at 2:1 (device off)	Multisite double blinded parallel design followed by open label	Hamilton depression rating scale. A responder was defined as a 40% reduction in the score	The study was designed to recruit 159 subjects to achieve 80% power for a 5% significance level. To allow for 20% dropout the study proposed to enroll 201 subjects. The preplanned analysis built in a placebo response allowing for 20% of controls vs. 40% of treatment to show a responder effect. Here, the sham control was tested for six months. A futility analysis of adequate power showed no group difference. The blind was confirmed to be adequate by asking the subject what group they thought they were in

we reviewed the peer-reviewed literature to identify the most commonly used designs in efficacy trials of FDA-approved neurostimulation devices and their control and sham elements.

While open-label studies are suitable for the preliminary study of new scES devices, they are inadequate to support the eventual translation of new devices into clinical practice. Open-label designs are highly susceptible to bias and placebo-linked phenomena, including variations of the observer effect known as the Hawthorne effect that renders isolation of a therapeutic effect difficult (81). Notably, it has been shown that the intensity of follow-up itself can improve outcomes (82). Thus, it is important that comparison groups are designed to isolate the effects of invasive stimulation to the greatest extent reasonably possible.

Designs advanced to accomplish this important objective include the two-arm parallel implant design (Fig. 2b). However, this design does not control for effects of the stimulation itself that is important for endpoints that have several contributing factors such as pain reduction in scES. In such scenarios, a third arm

or group can be added with or without crossover (Fig. 2f). The cohort is randomized into active, inactive (silent), subliminal, or sham (ineffective) stimulation, as has been utilized in some clinical trials of scES for pain (83,84). Variations of this design may include converting the inactive implants and/or the sham stimulation to active/targeted stimulation after the crossover point. The disadvantage of including a third arm is the increase in sample size requirement and duration of the trial. However, an efficient design for including both a silent implant and a sham stimulation control could allow for all implanted participants to undergo a period of silent implant testing to collect baseline data prior to randomization. Following the silent implant stage, participants are randomized into active versus sham stimulation groups (Fig. 2g). ''Active'' here means a stimulation configuration that targets the primary outcome, whereas sham stimulation uses stimulation parameters and configurations that are not expected to influence the primary outcomes. Depending on study goals, the sham group can cross over to the active stimulation group after a predetermined stimulation period. This design allows for testing and comparison of silent implants, active stimulation, and sham stimulation in one protocol.

There are specific issues for the enrollment of SCI participants to scES treatment crossover studies. In our experience, some participants state that they do not want to discontinue stimulation after they have experienced the benefits. Therefore, crossover designs that involve crossing from active to inactive implant states may be difficult to implement. Typically, participants agree to enroll with an expectation that they will eventually receive an active implant.

ENDPOINTS AND STIMULATION CONFIGURATIONS

The precise mechanisms and predicted effects of different scES parameter configurations have yet to be fully elucidated. Further, the interplay of stimulation with the methods and intensity of neurorehabilitation are important design considerations. This requires extra care not only in designing active vs. sham scES configurations but also in selecting primary and secondary endpoints for scES trials. Selected endpoints should be well validated with robust measurement properties with relevance to domains considered important by individuals with SCI. This consideration makes changes in blood pressure an attractive endpoint. Composite endpoints that assess effects across multiple systems may have particular value to measure the homeostatic normalization that has been described by research participants. Such endpoints, however, will require development. A consensus as to the most effective stimulation methodologies, for example, tonic vs. bursting, has yet to be achieved but would benefit the field to increase the comparability of studies.

ADAPTIVE TRIAL DESIGN CONSIDERATIONS FOR scES

Methods to increase clinical trial efficiency are necessary to both maximize the benefit/risk equation and to reduce costs (85). In 2016, the FDA issued specific guidance for Adaptive Designs for Medical Device Clinical Studies (86), defining an adaptive design for a clinical study of a medical device as ''*a clinical study design that allows for prospectively planned modifications based on accumulating study data without undermining the study's integrity and validity*.'' Such designs are helpful when there is substantial uncertainty regarding treatment vs. placebo differences in the primary endpoint and the expected variance. By incorporating planned data ''looks'' modeled to maintain the conditional rejection probability with a 5% type 1 error rate, the study power associated with an interim decision such as accepting or rejecting the null hypotheses can be determined and the trial adjusted for sample size with consideration of the adequacy of safety data. Further, the envisioned scenarios for the primary outcome measure can be modeled extensively to create probable confidence intervals. An established trial adaptation is a *blinded* interim analysis where the overall trial variance in the primary endpoint is ascertained and compared to that which was anticipated. DBS trial designs have been modeled in this manner (87,88).

One interesting application of an adaptive trial design for scES in SCI could be the determination of permanent effects. If evident, what durations and doses of scES are required? Adaptive designs modeled on the dose-effect could be utilized for such questions, which are especially valuable when predictive (89) and response biomarkers are available (90). Brain neuromodulation is amenable to biomarker-driven feedback, such as the use of recorded local field potential beta activity (91) to regulate the need for high-frequency stimulation in DBS for Parkinson's disease (92,93). The efficacy of spinal cord scES for pain has been linked to effective Aβ dorsal column fiber stimulation amplitudes, identified as a neurophysiological biomarker (94). Predictive biomarkers need to be developed for spinal restorative neuromodulation (95) and an important question is whether instantaneously evident and reversible effects such as a change in blood pressure or ability to move a joint predict longer-term benefits. Given the expense of neuromodulation studies, Bayesian approaches may be necessary. In a Bayesian hierarchical model, prior data may be combined with the data from a current study to update probability estimates progressively.

RESPONDER ANALYSES

Data from past and future studies of scES for SCI should be combined and analyzed to determine the demographic and biological characteristics of optimal scES responders. For example, the effects of injury architecture (96) and the impact of chronic changes in muscle and bone metabolism resulting from nerve dysfunction are important both for safety and efficacy in SCI neuromodulation studies. Determining these and other responder traits would improve the design of early and late-stage trials. In earlier-stage trials, it is sensible to include participants in whom safety is likely and in whom a large effect size is more probable. Once such proof-of-concept studies are completed, further responder analysis can be used to rationally conduct later-stage studies in a population with extended inclusion boundaries (97). It is essential for all groups performing scES trials to collaboratively build a responder database from which to learn valuable lessons.

LONG-TERM EFFECTS

Neuromodulation likely leads to circuit remodeling. Some effects may eventually persist in the off-stimulation state, as

shown by Jackson et al. for cortical stimulation (98) and by Cunningham and colleagues after testing a retinal prosthesis in blind subjects (99). It is important to design into scES trials for SCI mechanisms to acquire long-term assessments or follow-up studies, beginning with the consent and subject education.

CLINICAL DEVICE TRIALS WITH AND WITHOUT REHABILITATION

The study designs discussed above are applicable to trial designs with or without rehabilitation. In our opinion, physical neurorehabilitation is an essential component of any restorative scES therapy to guide activity-dependent neuroplasticity. But to scientifically validate this opinion, further studies and study designs will be needed to attempt to distinguish the effects of scES from the effects of rehabilitation. One fact we have already learned is that in all the individuals with chronic motor-complete SCI who have undergone scES implantation at our center, extensive physical rehabilitation alone prior to surgery did not lead to any meaningful improvements.

SUMMARY

It is clear that open-label device trials do not sufficiently control for placebo and Hawthorne effects. In non-SCI conditions such as Parkinson's Disease and chronic pain, most neuromodulatory trials have used a single or double crossover design with inactive implants as controls. Prior studies have established that placebo effects should be anticipated to occur in both the treatment and control groups. Blinding is challenging to achieve for scES trials, and in all of the study designs listed in Fig. 2, neither the participants nor the investigators are completely blinded. However, blinding of data assessors is essential for the primary outcome measures. Maximum attempts to reduce bias are needed; otherwise, premature or erroneous conclusions may be drawn regarding the efficacy and effectiveness of scES approaches as neurorestorative therapies for SCI. Adherence to these design principles will increase the rigor of future scES studies, which are necessary to develop the evidence basis for regulatory approval of scES to restore neurological function. If scES studies can be adequately controlled, a subsequent generation of studies may assess the use of combined therapeutic programs or modalities such as rehabilitative therapies.

CONCLUSION

Spinal cord epidural stimulation represents an emerging therapy for multi-functional recovery after SCI. Thus far, effects in several physiological systems are apparent. Clinical trials of implanted neuromodulation devices are susceptible to several placebo and observation-induced effects that can influence the evaluation of efficacy and differ from concerns and challenges in pharmacological trials. We recommend careful consideration of these potential biases in the design of controlled studies. The research designs discussed may be utilized for clinical trials to test for the efficacy of scES in multicenter studies. Based on our analysis, it would be most effective to implant all enrolled subjects prior to randomization and then compare active to inactive or suitable sham stimulation paradigms with suitably timed crossover.

Acknowledgements

Dr. Maxwell Boakye's efforts were supported by the Kentucky Spinal Cord Injury Center and the Ole A., Mabel Wise & Wilma Wise Nelson Endowment. Dr. Guest receives salary support from the Miami Project to Cure Paralysis. Dr. Ona Bloom's efforts were funded by New York State Spinal Cord Injury Research Board.

Authorship Statements

All authors reviewed the study designs, figures and tables. Dr. Boakye prepared the manuscript draft with important intellectual input from all authors. All authors approved the final manuscript.

How to Cite this Article:

Boakye M., Ugiliweneza B., Madrigal F., Mesbah S., Ovechkin A., Angeli C., Bloom O., Wecht J.W., Ditterline B., Harel N.Y., Kirshblum S., Forrest G., Wu S., Harkema S., Guest J. 2021. Clinical Trial Designs for Neuromodulation in Chronic Spinal Cord Injury Using Epidural Stimulation. Neuromodulation 2021; E-pub ahead of print. DOI:10.1111/ner.13381

REFERENCES

1. National Spinal Cord Injury Statistical Center. *Facts and figures at a glance*. Birmingham, AL: University of Alabama at Birmingham, 2020.
2. Armour BS, Courtney-Long EA, Fox MH, Fredine H, Cahill A. Prevalence and causes of paralysis-United States, 2013. *Am J Public Health* 2016;106:1855–1857.
3. Readdy WJ, Chan AK, Matijakovich DJ, Dhall SD. A review and update on the guidelines for the acute non-operative management of cervical spinal cord injury. *J Neurosurg Sci* 2015;59:119–128.
4. Yue JK, Chan AK, Winkler EA, Upadhyayula PS, Readdy WJ, Dhall SS. A review and update on the guidelines for the acute management of cervical spinal cord injury - part II. *J Neurosurg Sci* 2016;60:367–384.
5. Ahuja CS, Fehlings M. Concise review: bridging the gap: novel neuroregenerative and neuroprotective strategies in spinal cord injury. *Stem Cells Transl Med* 2016;5: 914–924.
6. Angeli CA, Edgerton VR, Gerasimenko YP, Harkema SJ. Altering spinal cord excitability enables voluntary movements after chronic complete paralysis in humans. *Brain* 2014;137:1394–1409.
7. Calvert JS, Grahn PJ, Zhao KD, Lee KH. Emergence of epidural electrical stimulation to facilitate sensorimotor network functionality after spinal cord injury. *Neuromodulation* 2019;22:244–252.
8. Harkema S, Gerasimenko Y, Hodes J et al. Effect of epidural stimulation of the lumbosacral spinal cord on voluntary movement, standing, and assisted stepping after motor complete paraplegia: a case study. *Lancet* 2011;377: 1938–1947.
9. Wagner FB, Mignardot JB, Le Goff-Mignardot CG et al. Targeted neurotechnology restores walking in humans with spinal cord injury. *Nature* 2018;563:65–71.
10. Darrow D, Balser D, Netoff TI et al. Epidural spinal cord stimulation facilitates immediate restoration of dormant motor and autonomic supraspinal pathways after chronic neurologically complete spinal cord injury. *J Neurotrauma*. 2019;36: 2325–2336.
11. Grahn PJ, Lavrov IA, Sayenko DG et al. Enabling task-specific volitional motor functions via spinal cord neuromodulation in a human with paraplegia. *Mayo Clin Proc* 2017;92:544–554.
12. Angeli CA, Boakye M, Morton RA et al. Recovery of over-ground walking after chronic motor complete spinal cord injury. *N Engl J Med* 2018;379:1244–1250.
13. Gill ML, Grahn PJ, Calvert JS et al. Neuromodulation of lumbosacral spinal networks enables independent stepping after complete paraplegia. *Nat Med* 2018; 24:1677–1682.
14. Harkema SJ, Wang S, Angeli CA et al. Normalization of blood pressure with spinal cord epidural stimulation after severe spinal cord injury. *Front Hum Neurosci.* 2018;12:83.

15. Aslan SC, Legg Ditterline BE, Park MC et al. Epidural spinal cord stimulation of lumbosacral networks modulates arterial blood pressure in individuals with spinal cord injury-induced cardiovascular deficits. *Front Physiol* 2018;9:565.
16. West CR, Phillips AA, Squair JW et al. Association of epidural stimulation with cardiovascular function in an individual with spinal cord injury. *JAMA Neurol* 2018; 75:630–632.
17. Harkema SJ, Legg Ditterline B, Wang S et al. Epidural spinal cord stimulation training and sustained recovery of cardiovascular function in individuals with chronic cervical spinal cord injury. *JAMA Neurol* 2018;75:1569–1571.
18. Herrity AN, Williams CS, Angeli CA, Harkema SJ, Hubscher CH. Lumbosacral spinal cord epidural stimulation improves voiding function after human spinal cord injury. *Sci Rep* 2018;8:8688.
19. Walter M, Lee AHX, Kavanagh A, Phillips AA, Krassioukov AV. Epidural spinal cord stimulation acutely modulates lower urinary tract and bowel function following spinal cord injury: a case report. *Front Physiol* 2018;9:1816.
20. Deer TR, Stewart CD. Complications of spinal cord stimulation: identification, treatment, and prevention. *Pain Med* 2008;9:S93–S101.
21. Taccola G, Barber S, Horner PJ, Bazo HAC, Sayenko D. Complications of epidural spinal stimulation: lessons from the past and alternatives for the future. *Spinal Cord* 2020;58:1049–1059.
22. Moeschler SM, Warner NS, Lamer TJ et al. Bleeding complications in patients undergoing percutaneous spinal cord stimulator trials and implantations. *Pain Med* 2016;17:2076–2081.
23. Babu R, Hazzard MA, Huang KT et al. Outcomes of percutaneous and paddle lead implantation for spinal cord stimulation: a comparative analysis of complications, reoperation rates, and health-care costs. *Neuromodulation.* 2013;16:418–426.discussion 26-7.
24. Bendersky D, Yampolsky C. Is spinal cord stimulation safe? A review of its complications. *World Neurosurg* 2014;82:1359–1368.
25. Eldabe S, Buchser E, Duarte RV. Complications of spinal cord stimulation and peripheral nerve stimulation techniques: a review of the literature. *Pain Med* 2016;17:325–336.
26. Arnold FW, Bishop S, Johnson D et al. Root cause analysis of epidural spinal cord stimulator implant infections with resolution after implementation of an improved protocol for surgical placement. *J Infect Prev* 2019;20:185–190.
27. Legg Ditterline BE, Wade S, Ugiliweneza B et al. Beneficial cardiac structural and functional adaptations after lumbosacral spinal cord epidural stimulation and task-specific interventions: a pilot study. *Front Neurosci* 2020;14:554018.
28. Pettigrew RI, Heetderks WJ, Kelley CA et al. Epidural spinal stimulation to improve bladder, bowel, and sexual function in individuals with spinal cord injuries: a framework for clinical research. *IEEE Trans Biomed Eng* 2017;64:253–262.
29. Rejc E, Angeli C, Harkema S. Effects of lumbosacral spinal cord epidural stimulation for standing after chronic complete paralysis in humans. *PLoS One* 2015;10: e0133998.
30. Fort DG, Herr TM, Shaw PL, Gutzman KE, Starren JB. Mapping the evolving definitions of translational research. *J Clin Transl Sci* 2017;1:60–66.
31. Woolf SH. The meaning of translational research and why it matters. *JAMA* 2008; 299:211–213.
32. Deuschl G, Schade-Brittinger C, Krack P et al. A randomized trial of deep-brain stimulation for Parkinson's disease. *N Engl J Med* 2006;355:896–908.
33. Frank SA, Wilson R, Holloway RG et al. Ethics of sham surgery: perspective of patients. *Mov Disord* 2008;23:63–68.
34. Kim SY, Frank S, Holloway R, Zimmerman C, Wilson R, Kieburtz K. Science and ethics of sham surgery: a survey of Parkinson disease clinical researchers. *Arch Neurol* 2005;62:1357–1360.
35. Freeman TB, Vawter DE, Leaverton PE et al. Use of placebo surgery in controlled trials of a cellular-based therapy for Parkinson's disease. *N Engl J Med* 1999;341:988–992.
36. NIH's Definition of a Clinical Trial: National Institutes of Health; 2016 https://grants.nih.gov/policy/clinical-trials/definition.htm
37. Berlin JA, Golub RM. Meta-analysis as evidence: building a better pyramid. *JAMA* 2014;312:603–605.
38. Suresh K. An overview of randomization techniques: an unbiased assessment of outcome in clinical research. *J Hum Reprod Sci* 2011;4:8–11.
39. Lin Y, Zhu M, Su Z. The pursuit of balance: an overview of covariate-adaptive randomization techniques in clinical trials. *Contemp Clin Trials.* 2015;45:21–25.
40. Lim CY, In J. Randomization in clinical studies. *Korean J Anesthesiol* 2019;72:221–232.
41. Rubin DB. The design versus the analysis of observational studies for causal effects: parallels with the design of randomized trials. *Stat Med* 2007;26:20–36.
42. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;273:408–412.
43. Saltaji H, Armijo-Olivo S, Cummings GG, Amin M, da Costa BR, Flores-Mir C. Influence of blinding on treatment effect size estimate in randomized controlled trials of oral health interventions. *BMC Med Res Methodol* 2018;18:42.
44. Impact of blinding on estimated treatment effects in randomised clinical trials: meta-epidemiological study. *BMJ.* 2020;368:m358.
45. Skelly AC, Dettori JR, Brodt ED. Assessing bias: the importance of considering confounding. *Evid Based Spine Care J* 2012;3:9–12.
46. Wartolowska K, Judge A, Hopewell S et al. Use of placebo controls in the evaluation of surgery: systematic review. *BMJ* 2014;348:g3253.
47. Sutherland ER. Sham procedure versus usual care as the control in clinical trials of devices: which is better? *Proc Am Thorac Soc* 2007;4:574–576.
48. Cobb LA, Thomas GI, Dillard DH, Merendino KA, Bruce RA. An evaluation of internal-mammary-artery ligation by a double-blind technic. *N Engl J Med* 1959; 260:1115–1118.
49. Moseley JB, O'Malley K, Petersen NJ et al. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. *N Engl J Med* 2002;347:81–88.
50. Meissner K, Fässler M, Rücker G et al. Differential effectiveness of placebo treatments: a systematic review of migraine prophylaxis. *JAMA Intern Med* 2013;173: 1941–1951.
51. Kaptchuk TJ, Goldman P, Stone DA, Stason WB. Do medical devices have enhanced placebo effects? *J Clin Epidemiol* 2000;53:786–792.
52. Freed CR, Greene PE, Breeze RE et al. Transplantation of embryonic dopamine neurons for severe Parkinson's disease. *N Engl J Med* 2001;344:710–719.
53. Olanow CW, Goetz CG, Kordower JH et al. A double-blind controlled trial of bilateral fetal nigral transplantation in Parkinson's disease. *Ann Neurol* 2003;54: 403–414.
54. Al-Kaisy A, Royds J, Palmisani S et al. Multicentre, double-blind, randomised, sham-controlled trial of 10 khz high-frequency spinal cord stimulation for chronic neuropathic low back pain (MODULATE-LBP): a trial protocol. *Trials* 2020; 21:111.
55. Al-Kaisy A, Palmisani S, Pang D et al. Prospective, randomized, sham-control, double blind, crossover trial of subthreshold spinal cord stimulation at various kilohertz frequencies in subjects suffering from failed Back surgery syndrome (SCS frequency study). *Neuromodulation.* 2018;21:457–465.
56. Williams A, Gill S, Varma T et al. Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): a randomised, open-label trial. *Lancet Neurol* 2010;9:581–591.
57. Holtzheimer PE, Husain MM, Lisanby SH et al. Subcallosal cingulate deep brain stimulation for treatment-resistant depression: a multisite, randomised, sham-controlled trial. *Lancet Psychiatry* 2017;4:839–849.
58. Hauptman PJ, Gottlieb SS. Clinical trial design in contemporary device studies in heart failure: is there a gold standard? *J Card Fail* 2014;20:223–228.
59. Duarte RV, Nevitt S, McNicol E et al. Systematic review and meta-analysis of placebo/sham controlled randomised trials of spinal cord stimulation for neuropathic pain. *Pain* 2020;161:24–35.
60. De Ridder D, Plazier M, Kamerling N, Menovsky T, Vanneste S. Burst spinal cord stimulation for limb and back pain. *World Neurosurg.* 2013;80:642–9.e1.
61. Kriek N, Groeneweg JG, Stronks DL, de Ridder D, Huygen FJ. Preferred frequencies and waveforms for spinal cord stimulation in patients with complex regional pain syndrome: a multicentre, double-blind, randomized and placebo-controlled crossover trial. *Eur J Pain* 2017;21:507–519.
62. Meier K, Nikolajsen L, Sørensen JC, Jensen TS. Effect of spinal cord stimulation on sensory characteristics: a randomized, blinded crossover study. *Clin J Pain* 2015;31:384–392.
63. Perruchoud C, Eldabe S, Batterham AM et al. Analgesic efficacy of high-frequency spinal cord stimulation: a randomized double-blind placebo-controlled study. *Neuromodulation.* 2013;16:363–369.discussion 9.
64. Schu S, Slotty PJ, Bara G, von Knop M, Edgar D, Vesper J. A prospective, randomised, double-blind, placebo-controlled study to examine the effectiveness of burst spinal cord stimulation patterns for the treatment of failed back surgery syndrome. *Neuromodulation* 2014;17:443–450.
65. Tjepkema-Cloostermans MC, de Vos CC, Wolters R, Dijkstra-Scholten C, Lenders MW. Effect of burst stimulation evaluated in patients familiar with spinal cord stimulation. *Neuromodulation* 2016;19:492–497.
66. Wolter T, Kiemen A, Porzelius C, Kaube H. Effects of sub-perception threshold spinal cord stimulation in neuropathic pain: a randomized controlled double-blind crossover study. *Eur J Pain* 2012;16:648–655.
67. Wolter T, Winkelmuller M. Continuous versus intermittent spinal cord stimulation: an analysis of factors influencing clinical efficacy. *Neuromodulation* 2012;15: 13–19.discussion 20.
68. Dougherty DD, Rezai AR, Carpenter LL et al. A randomized sham-controlled trial of deep brain stimulation of the ventral capsule/ventral striatum for chronic treatment-resistant depression. *Biol Psychiatry* 2015;78:240–248.
69. Bergfeld IO, Mantione M, Hoogendoorn ML et al. Deep brain stimulation of the ventral anterior limb of the internal capsule for treatment-resistant depression: a randomized clinical trial. *JAMA Psychiat* 2016;73:456–464.
70. Kisely S, Li A, Warren N, Siskind D. A systematic review and meta-analysis of deep brain stimulation for depression. *Depress Anxiety* 2018;35:468–480.
71. Mann JM, Foote KD, Garvan CW et al. Brain penetration effects of microelectrodes and DBS leads in STN or GPi. *J Neurol Neurosurg Psychiatry* 2009;80: 794–797.
72. Okun MS, Gallo BV, Mandybur G et al. Subthalamic deep brain stimulation with a constant-current device in Parkinson's disease: an open-label randomised controlled trial. *Lancet Neurol* 2012;11:140–149.
73. Tykocki T, Nauman P, Koziara H, Mandat T. Microlesion effect as a predictor of the effectiveness of subthalamic deep brain stimulation for Parkinson's disease. *Stereotact Funct Neurosurg* 2013;91:12–17.
74. Wright MS. A case for randomized, double-blinded, sham-controlled. Class III medical device trials. *Yale Law Policy Rev* 2016;34:199–213.
75. North R, Eldabe S. Neuromodulation device comparison studies come of age. *Pain Med* 2017;18:2261–2262.
76. Carome MA. Implanted spinal cord stimulators for pain relief. Public Citizen; 2020. https://www.citizen.org/wp-content/uploads/2526_200610_Spinal-Cord-Stimulator-Report_FINAL.pdf?eType=EmailBlastContent&eId=765162c2-baeb-41db-a6ae-0694813ad96c
77. Lauer M, Barker JP, Solano M, Dubin J. FDA device regulation. *Mo Med* 2017;114: 283–288.
78. Bhatt DL, Kandzari DE, O'Neill WW et al. A controlled trial of renal denervation for resistant hypertension. *N Engl J Med* 2014;370:1393–1401.

79. Bakris GL, Townsend RR, Liu M et al. Impact of renal denervation on 24-hour ambulatory blood pressure: results from SYMPLICITY HTN-3. *J Am Coll Cardiol* 2014;64:1071–1078.
80. Mücke D, Hermes A, Roettger TB et al. The effects of thalamic deep brain stimulation on speech dynamics in patients with essential tremor: an articulographic study. *PLoS one* 2018;13:e0191359-e.
81. Parsons HM. What happened at Hawthorne? new evidence suggests the Hawthorne effect resulted from operant reinforcement contingencies. *Science* 1974; 183:922–932.
82. McCarney R, Warner J, Iliffe S, van Haselen R, Griffin M, Fisher P. The Hawthorne effect: a randomised, controlled trial. *BMC Med Res Methodol* 2007; 7:30.
83. Eddicks S, Maier-Hauff K, Schenk M, Muller A, Baumann G, Theres H. Thoracic spinal cord stimulation improves functional status and relieves symptoms in patients with refractory angina pectoris: the first placebo-controlled randomised study. *Heart (British Cardiac Society)* 2007;93:585–590.
84. Lanza GA, Grimaldi R, Greco S et al. Spinal cord stimulation for the treatment of refractory angina pectoris: a multicenter randomized single-blind study (the SCS-ITA trial). *Pain* 2011;152:45–52.
85. Mulcahey MJ, Jones LAT, Rockhold F et al. Adaptive trial designs for spinal cord injury clinical trials directed to the central nervous system. *Spinal Cord* 2020;58: 1235–1248.
86. Administration FaD. Adaptive designs for medical device clinical studies. Guidance for Industry and Food and Drug Administration Staff 2016.
87. Brannath W, Mehta CR, Posch M. Exact confidence bounds following adaptive group sequential tests. *Biometrics* 2009;65:539–546.
88. Mehta CR, Bauer P, Posch M, Brannath W. Repeated confidence intervals for adaptive group sequential trials. *Stat Med* 2007;26:5422–5433.
89. Mesbah S, Gonnelli F, Angeli CA, El-Baz A, Harkema SJ, Rejc E. Neurophysiological markers predicting recovery of standing in humans with chronic motor complete spinal cord injury. *Sci Rep* 2019;9:14474.
90. Alam M, Garcia-Alias G, Jin B et al. Electrical neuromodulation of the cervical spinal cord facilitates forelimb skilled function recovery in spinal cord injured rats. *Exp Neurol* 2017;291:141–150.
91. Little S, Pogosyan A, Neal S et al. Adaptive deep brain stimulation in advanced Parkinson disease. *Ann Neurol* 2013;74:449–457.
92. Meidahl AC, Tinkhauser G, Herz DM, Cagnan H, Debarros J, Brown P. Adaptive deep brain stimulation for movement disorders: the Long road to clinical therapy. *Mov Disord* 2017;32:810–819.
93. Hoang KB, Cassar IR, Grill WM, Turner DA. Biomarkers and stimulation algorithms for adaptive brain stimulation. *Front Neurosci.* 2017;11:564.
94. Parker JL, Karantonis DM, Single PS, Obradovic M, Cousins MJ. Compound action potentials recorded in the human spinal cord during neurostimulation for pain relief. *Pain* 2012;153:593–601.
95. Mesbah S, Ball T, Angeli C et al. Predictors of volitional motor recovery with epidural stimulation in individuals with chronic spinal cord injury. *Brain* 2020;144: 420–433.
96. Rejc E, Smith AC, Weber KA 2nd et al. Spinal cord imaging markers and recovery of volitional leg movement with spinal cord epidural stimulation in individuals with clinically motor complete spinal cord injury. *Front Syst Neurosci* 2020;14:559313.
97. Pallmann P, Bedding AW, Choodari-Oskooei B et al. Adaptive designs in clinical trials: why use them, and how to run and report them. *BMC Med.* 2018;16:29.
98. Jackson A, Mavoori J, Fetz EE. Long-term motor cortex plasticity induced by an electronic neural implant. *Nature* 2006;444:56–60.
99. Cunningham SI, Shi Y, Weiland JD et al. Feasibility of structural and functional MRI acquisition with unpowered implants in Argus II retinal prosthesis patients: a case study. *Transl Vis Sci Technol.* 2015;4:6.

COMMENTS

The reports in the literature describing the outcomes of various approaches to spinal cord epidural stimulation (scES) are, at the same time, both exciting and confounding. The mechanism of action is unknown and might be different for some of the different outcomes (e.g., motor vs. autonomic; immediate vs. late effects; etc.). The optimum electrode locations and stimulation parameters have yet to be established. The role of adjunctive therapy has yet to be determined. Given these and other unanswered questions, it seems that the only way to begin to work through these issues will be to conduct well-designed controlled studies. This paper presents a well-reasoned argument for the proposed study design. Now we anticipate future studies based on these principles that should provide us with a clear understanding of how and when scES should be applied to consistently and reliably achieve the impressive results that have been reported.

Kevin Kilgore, PhD
Cleveland, OH USA

***

This is clearly an important topic and the design of a randomized control trial studying the efficacy of epidural spinal cord stimulation for chronic spinal cord injury must be well thought out in order for the results to be accepted by the scientific community. The authors propose and make a compelling argument for a single crossover design where patients are screened and undergo implantation of a spinal cord stimulator prior to being randomized to either active or inactive stimulation groups. The inactive group will then crossover to the active group. Such a design will mitigate ethical implications of having a control group with a "sham" stimulator that provides no benefit to the patient.

Royce Woodroffe, MD
Iowa City, IA USA

