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Epidural Spinal Stimulation to Improve Bladder, Bowel, and Sexual Function in Individuals with Spinal Cord Injuries: A Framework for Clinical Research

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Abstract

While some recent studies that apply epidural spinal cord stimulation (SCS) have demonstrated a breakthrough in improvement of the health and quality of the life of persons with spinal cord injury (SCI), the numbers of people who have received SCS are small. This is in sharp contrast to the thousands of persons worldwide living with SCI who have no practical recourse or hope of recovery of lost functions. Thus, the vision is to understand the full potential of this new intervention and to determine if it is safe and effective in a larger cohort, and if it is scalable so that it can be made available to all those who might benefit. To achieve this vision, the National

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Institute of Biomedical Imaging and Bioengineering (NIBIB) called for and organized a consortium of multiple stakeholder groups: foundations addressing paralysis, Federal and public agencies, industrial partners, academicians and researchers, all interested in the same goal. Based on input from consortium participants, we have reasoned that a first step is to define a scalable SCS approach that is effective in restoring lost autonomic physiology, specifically bladder, bowel and sexual function. These functions are most critical for improving the quality of life of persons living with SCI. This report outlines a framework for conducting the research needed to define such an effective SCS procedure that might seek FDA approval and be implemented at the population level.

Index Terms

Epidural spinal cord stimulation; spinal cord injury; autonomic nervous system dysfunctions; spinal mapping for bladder; bowel and sexual functions; paralysis; interventions for spinal cord injuries

SECTION I INTRODUCTION

The successful application of epidural spinal cord stimulation (SCS) to reduce paralysis in a small number of persons with spinal cord injury (SCI) has provided hope for recovery of lost functions in individuals with SCI. This hope has reached hundreds of thousands of individuals with paralysis from SCI in the U.S. and throughout the world [1]. Although the numbers of those who have been treated and have benefitted from SCS are small, there is sufficient evidence to encourage further research on making this intervention safe and effective for all persons with SCI.

In 2011, Harkema et al. reported the first-in-man application of SCS in a person with motor complete SCI which resulted in full weight-bearing standing and some lower extremity voluntary motion [2]. Also, the patient experienced functional improvement in bladder, bowel and sexual function and temperature regulation. The patient is now able to voluntarily void his bladder with minimum residual volume and has reported improved sexual response and performance [2]. Angeli et al. reported a study of four persons with motor complete SCI who experienced voluntary control of paralyzed muscles with SCS [3]. She states, “We have uncovered a fundamentally new intervention strategy that can dramatically affect recovery of voluntary movement in individuals with complete paralysis even years after injury” [3]. Her patients also reported functional improvements in bladder, bowel and sexual functions. To further study the underlying factors that improve bladder control, Gad et al. examined bladder voiding with SCS in paralyzed, step trained rats [4]. SCS appeared to activate locomotor-related spinal neuronal circuits and influence the neural networks controlling bladder function. Following the report by Angeli, the Director of the National Institute of Biomedical Imaging and Bioengineering (NIBIB) stated “…Our vision is to make this new intervention available to all who might benefit.”

The number of persons in 2013 in the U.S. with SCI has been estimated at approximately 300,000 (https://www.nscisc.uab.edu/PublicDocuments/fact_figures_docs/Facts%202013.pdf). Although the incidence of SCI has remained relatively stable during the last

decade (53 to 54 cases per 1 million population), there has been a modest increase in the overall absolute number of cases of SCI from 1993 to 2012 apparently related to the growth in population[1]. In 2009, the ratio of males to females was 4.2/1, or 80.9% of SCI occurring among males (National Spinal Cord Injury Statistical Center (NSCISC). A recent state of Oklahoma study on SCI by age, reported incidence rates of spinal cord injury were highest in the male 20- to 24-year-old population (annual rate, 144 cases/million) followed by the male 15- to 19-year-old population. It is interesting to note that spinal cord injury incidence rates have substantially increased over time in the 65- to 74-year-old and 75- to 84-year-old age groups. This now accounts for a larger proportion of total spinal cord injury cases because of the increasing elderly population [1].

To help better define and make this emerging technology more widely available, NIBIB called for the creation of a Consortium of those who similarly envision addressing paralysis due to SCI. This began by leading a series of meetings from November 2014 to June 2015 with key academic, industry, patient advocacy, government and medical leaders who organized to form such a group and deliberate on options for a path forward. The goals of the meetings were: (1) to explore strategies for marshalling complementary talents and resources (2) to identify the next steps required to accelerate this research, and (3) ultimately to optimize the delivery of SCS as an intervention for persons with SCI.

The recent studies employing SCS in individuals with SCI were based upon many years of animal research [5 – 7]. These were initiated with a primary goal of improving stepping and/or standing in persons who were at least two years beyond their injury and had no ability to move any key muscle groups below the level of injury [8 – 14]. As has been reported, an unexpected outcome was the return of some voluntary control of movements below the site of injury. This finding was previously not reported for this population. Notably, while these voluntary movements did not enable control of locomotor function, the individual reports from all participants suggested that the epidural stimulation had profound and meaningful benefits on other adverse health conditions associated with SCI. These included alleviating autonomic dysfunction in bladder, bowel and sexual response and the secondary complications associated with these dysfunctions [5]. The Consortium noted that the ability to generate complex and coordinated locomotor movement using SCS in persons with SCI is an extremely challenging long-term goal. It is costly and requires extensive time and effort by both SCI patients and researchers. We have reasoned, therefore, that as a next step, researchers studying the application of SCS for SCI should focus on examining the conditions for alleviating autonomic dysfunction. Such a study could potentially provide a feasible initial step for determining safety and efficacy of SCS on health related outcomes, using existing devices for stimulation. Bladder, bowel and sexual dysfunction were chosen as an initial focus of this endeavor as these have been identified as the most significant factors that negatively impact quality of life for those with SCI [12], [13]. In addition to limiting an individual’s autonomy and ability to engage socially, bladder dysfunction and complications associated with chronic and intermittent catheterization frequently lead to serious clinical conditions, including urinary tract infections, urinary incontinence, calculi, bladder cancer, and renal dysfunction. Such adverse outcomes result in hospital admissions and increase the risk of premature death [14 – 18].

Based on the participant reports and the known interactions between spinal circuits that modulate bladder function and those that affect bowel and sexual function, we have reasoned that all three systems, bladder, bowel and sexual dysfunction, should be studied in parallel in a prospective study [19]. Moreover, prior to initiation of any pivotal trial of this novel intervention, one or more smaller pilot studies would be valuable to identify the epidural spinal stimulation parameters that could be associated with improved bladder, bowel, and sexual function in individuals with SCI. This paper summarizes the deliberations of a broad group of stakeholders for consideration in designing such a study.

Approach

NIBIB convened a group of academic, industry, patient advocacy, foundations and medical leaders in a workshop entitled “Addressing Paralysis through Spinal Stimulation Technologies,” which took place on November 15, 2014. The workshop was an unprecedented effort to gather experts from a wide range of disciplines and fields to discuss the key issues related to spinal stimulation for individuals with SCI. The attendees included researchers in basic and clinical neuroscience, machine learning, rehabilitation for neurological disorders, multi-electrode array technology, regulators, device manufacturers and leaders of foundations addressing paralysis for the purpose of determining the best path forward for epidural spinal stimulation research in SCI individuals given the current state of knowledge based on both animal and human research.

In preparation for the workshop, participants received copies of scientific publications pertinent to the topic [2], [3], [4], [10], [11], [20], [21], and [22]. The workshop began by discussing current epidural spinal stimulation technologies, outcomes from recent animal and human studies, and what is currently known about neurological deficits in persons with SCI. Representatives from device industries presented overviews of the technology employed in current SCS devices. Later in the meeting, participants were asked to prioritize conditions in individuals with SCI to be addressed and cohorts to be studied in future trials. They were also asked to define issues for consideration in determining stimulation parameters and clinical outcome measures based on the current technology. Two key outcomes were realized from the workshop: (1) the formation of a consortium of academic, industry, patient advocacy, foundation and medical leaders to facilitate greater communication and cooperation; and (2) the recognition that continued discussion and eventual prioritization of conditions, cohorts, stimulation techniques and parameters, and clinical assessment measurements are needed in order to develop a roadmap for future research and treatment delivery to SCI patients. Regular meetings were held to determine the best approach for developing clinical studies on epidural spinal stimulation to improve bladder, bowel, and sexual function in individuals with SCI. Over five months, discussions were held on key thematic topics that included (1) Interventions, Study Objectives, and Hypotheses, (2) Clinical Testing and Training, (3) Participant Selection and Length of Follow Up, and (4) End Points, Evaluation of Success, Safety and Anticipated Adverse Events.

This resulted in defining a framework for research that would describe the techniques and parameters that are most efficacious in objectively restoring bladder, bowel and sexual function.

Paper Organization—The collective perspective of the Consortium has been compiled into the following sections: Section II describes recommended interventions, study objectives (specific hypotheses are listed in the appendix), Section III discusses issues related to clinical testing and training; Section IV recommends procedures for stimulation mapping preliminary to clinical testing; Section V describes patient selection and recommendations for follow-up; Section VI refers to safety and anticipated adverse events; and Section VII summarizes the recommendations and discusses future considerations.

SECTION II Interventions and Study Objectives

Consortium members recommended that the initial intervention strategy be the use of epidural stimulation of the lumbar or sacral areas of the spinal cord (with electrodes covering the spinal levels from L1 to S3) in participants with SCI. While effective, the initial reported intervention details are thought to benefit from further optimization [23]. With input from investigators who have had experience with implanted study participants, the consensus opinion emphasized the importance of conducting stimulation mapping studies, using rapid onset metrics to evaluate the effective stimulation parameters and electrode locations for *each* study participant. This is important given that substantial functional differences exist among patients with SCI. For example, a previous study on improving standing in SCI individuals with SCS, emphasized that the different aspects of the desired motor output required different stimulation characteristics, including anode and cathode locations, pulse amplitude, and pulse frequencies. Also, the body position (supine, sitting or standing) influenced the specificity and function of the EMG responses [24]. Thus, different combinations of stimulation parameters are expected to be required to obtain the most effective conditions for these coordinated autonomic functions. Computational modeling and machine approaches could also be used to facilitate the optimization process and to explore the theoretical effects of changing stimulation parameters of location, intensity, and duration.

The group made recommendations for defining the scope of the initial clinical study design. Epidural stimulation was combined with locomotor training in the previous studies of SCS for individuals with SCI where autonomic function was substantially improved. To assess the effectiveness of SCS alone, however, there is a need to examine the impact of epidural spinal stimulation without locomotor training. To stay focused on the most compelling short-term opportunities, we reasoned that the objectives for the initial study should be to define the conditions for improving bladder, bowel, and sexual function collectively, as each has related and integrated neural pathways [19]. The following should be considered as potential outcome measures: increased bladder capacity, increased time between bladder emptying, increased ability to void voluntarily, reduction in urinary incontinence, reduced time needed for bowel management, reduction in fecal incontinence, and improved sexual function. Secondary outcomes should include improved health- related quality of life and well-being, such as participation in the community, social activities, and employment.

As the precise mechanisms underlying spinal epidural stimulation are still unknown, discussions were prompted about the need for completing further animal studies before proceeding with human studies. Discussants argued for pursuing both (1) additional animal studies to gain better understanding of the principles of function recovery and (2) pilot studies with humans to identify relevant parameters and define the benefit and safety in humans building on the promising results already observed. Animal studies provide insight into strategies that can be used to optimize interventions to promote motor and autonomic function and facilitate the translation to clinical human studies. Nonetheless, the parameters for biological activity and ultimately the efficacy of spinal stimulation technologies are best tested and established with direct studies in humans.

In discussing possible hypotheses of function, it was noted that the published studies demonstrated that epidural stimulation and motor training together could improve the ability of motor complete SCI persons to stand and step with assistance, and move the lower limbs voluntarily. Given the reports of improved bladder, bowel, and sexual function in the persons with complete SCI who received the intervention, it was suggested that the spinal and autonomic networks that generate the control of these systems might be reactivated to a more normal functional state. The role of enhancement through activity-dependent mechanisms was also considered. These include epidural stimulation of target interneuronal networks and/or the associated autonomic circuits or ganglia in concert with motor training (standing and stepping). Related mechanistic questions that focused on identifying (1) the specific nerve fibers and pathways recruited by the effective spinal cord stimulation parameters and (2) where those fibers project in the central nervous system to produce subsequent activation of circuits that affect muscle tone in sphincters and bladder, bowel, sexual, and other autonomic functions.

Neuroplasticity of these spinal cord circuits should also be considered, as it is known that injury leads to changes in circuit function and chronic stimulation can also produce changes. Thus, understanding the direct and immediate effects of SCS in addition to longer-term training effects will be important.

SECTION III Clinical Testing and Training

The consensus view about clinical testing and training was that a multi-disciplinary team will be critical in designing and conducting a meaningful spinal stimulation study. In particular, urologists and gastroenterologists should have a major role in the study design and execution. In addition, the team should include a full range of SCI clinical experts (SCI physiatrists, neurologists, neurosurgeons, radiologists, nurses, physical therapists, and rehabilitation psychologists), and critical input should be sought from neuroscientists, ethicists, regulatory specialists, statisticians, bioengineers, and people with SCI and their families or primary caregivers. Use of an experienced clinical study advisory board and an appropriate data and safety monitoring plan (DSMP) are highly recommended.

To achieve the study goals, it will be essential to obtain extensive baseline assessments of the participants prior to initiation of the intervention. These must be carefully considered to ensure inter-session and inter-rater reliability and to balance the need and desire to be

thorough with the limitations of time and fatigability of the participants and the study team. SCI clinical assessments should include documentation of the neurological status, bladder, bowel and sexual functional status, and the extent and nature of the injury. To facilitate data collection and sharing, use of the SCI common data elements [https://commondataelements.ninds.nih.gov/SCI.aspx#tab=Data_Standards] and the International SCI Data Sets [https://commondataelements.ninds.nih.gov/Doc/SCI/F0824_International_SCI_Pain_Basic_Data_Set.pdf] is recommended. These have been developed by multidisciplinary teams of clinical experts (See http://www.ncbi.nim.nih.gov/pubmed/16955072) [25].

Existing capabilities to document the anatomical characteristics of the injury site and the functional capacity of the spinal cord before and during epidural stimulation were recommended. This included preliminary analysis of various imaging strategies suitable for addressing the known challenges of SCI imaging, including artifacts due to vertebral stabilization hardware and physiologic motion [26].

Magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) guidelines and parameters have been developed by SCI radiologists as part of the National Institute of Neurological Diseases and Stroke common data element (CDE) project, and these can be found at the NINDS CDE website [https://commondataelements.ninds.nih.gov/#page=Default]. X-rays and CT could be used to precisely identify the location of electrodes and correlate with effectiveness. MRI compatible stimulation technology is evolving, and functional MRI (fMRI) for investigational research might be feasible as part of the study design, pending appropriate regulatory approvals. The current commercially available spinal stimulators are still contraindicated for MRI, as the artifacts may be problematic and risks of tissue heating in this application are still unknown [27]. Thus, careful imaging of the spinal cord should be completed before implantation of a stimulator. It is important to consider potential uses of functional spinal cord imaging to document activity patterns that might be altered by epidural stimulation. When available, MR compatible leads and stimulators should be strongly considered if they can enable post- implant functional MR studies. Indeed, resting state fMRI and DTI connectome tractography approaches show some promise for investigating mechanisms of stimulation device therapies in the brain [28]. However, functional imaging approaches are still exploratory for SCI and are limited by the size and other physical characteristics of the spinal cord such as magnetic susceptibility cord-vertebrae differences. The use of ultrasound can be an effective tool for assessing bladder volumes and upper urinary tract changes. Also, a wide variety of highly informational electrodiagnostic tests can be performed prior to and during the intervention phase of the study to provide a broad picture of the functional status of spinal tracts and reflexes.

Recommended baseline measures before implantation are found in Table 1.

For rapid preliminary assessment of changes in lower urinary tract function after stimulation, sphincter reflex measures should be considered with particular attention to bladder sphincter coordination during periods of urine storage and voiding. This will require urodynamic testing with a urethral pressure sensor, EMG and complete fluoroscopy.

In addition, quality of life measures should be obtained to assess the impact of the intervention on the health and well-being of the participant over time. The current SCI-QOL instrument [34] provides measures that assess such impact; this has become an essential consideration in determining the effectiveness of interventions.

Careful consideration should be given to medications that affect bladder, bowel, or sexual function. It is recommended that patients receiving anticholinergics and alpha blockers can be included in the study because these medications will have little effect on general volitional voiding and may help with bladder capacity as long as the dose is steady. However, those patients treated with onobotulinumtoxinA (Botox®) for urinary incontinence should be excluded from the study, as effects on bladder function can last for as long as one year after treatment.

SECTION IV Spinal Mapping for Bladder, Bowel, and Sexual Function

The use of epidural stimulation to modify autonomic spinal circuitry is in a very early exploratory phase and no detailed methodology has been published. Based on discussions with urology and neurology experts, the following reflect potential starting points suggested for examining and mapping the effects of SCS modulation on neural pathways or circuits that mediate and coordinate bladder, bowel, and sexual function. In the process of examining these functional parameters, it is anticipated that intermediate markers of activation will be identified that correlate with desired impact and thus could serve as biomarkers of target engagement for future stage clinical studies and trials.

For all studies, it was recommended to map and record the participant's response to stimulation along the four coordinates of location, recording amplitude, duration and frequency. It is important to identify the acute and long term effects of stimulation. There is a need to decide the optimal number of electrodes as well as the coverage of electrodes based on outcome.

The group suggested the following actions for identifying the neural pathways or sites that stimulate the bladder, bowel, and sexual function:

1. Initial broad localization of potential effective stimulation sites may be determined by identifying stimulation sites for activation of skeletal muscles that are known to be proximate to the spinal bladder nuclei;
2. These regions could be further refined by identifying electrode combinations and stimulation parameters, leading rapid onset and rapid offset responses that can be reproduced at short inter-stimulation intervals, such as time linked bladder wall EMG activity. These acute measures are preferable to examining the effect of stimulation on bladder filling and voiding responses, which are very slow processes [29, 30, 36 – 40]; it is important to note, however, that the latter responses may be differentially affected by SCS.
3. The location of sites and parameters that promote urine storage and continence may then be identified by recording phasic reflex bladder contractions in a partially filled bladder under isovolumetric conditions and then determining

which sites suppress these contractions to enable filling, or by recording sphincter EMG activity and determining which sites enhance this activity to maintain continence;

4. Mapping of spinal sites that promote voiding can be performed as tolerated by further filling the bladder. In the best case scenario, sites or patterns may be identified where stimulation does not interfere with the guarding reflex during filling, but enables continuous bladder contraction and sphincter relaxation during active voiding. In participants with detrusor-sphincter-dyssynergy it may be possible to use these parameters to train the bladder/sphincter to coordinate a voiding response. Because epidural stimulation may influence the activity of complex spinal circuitry, the longer term effects should be correlated with the rapid onset effects and included in the mapping process;

5. Subsequent studies can be similarly designed to identify patterns and parameters mediating bowel and anal sphincter coordination, erection and ejaculation. Mapping may also include modulation of thoracic and lumbosacral visceral reflexes by low level stimulation. The visceral reflexes include sympathetic pathways arising in the thorocolumbar segments of the spinal cord. Note that the modulation of sympathetic control of the bladder, urethra, distal bowel, anal canal and seminal emission could be an important component of epidural stimulation. In addition, suppression of autonomic dysreflexia may also involve modulation of thoracic and lumbar sympathetic pathways to blood vessels and heart;

6. While mapping of human subjects should be the focus of epidural spinal stimulation studies, animal studies can be beneficial for understanding effective procedural parameters of electrode location and stimulation patterns [41 –44].

Finally, there are limitations to the flexibility of commercial stimulation devices to produce patterns of stimulation that may be best for enabling autonomic function in SCI indications. Several commercial stimulators have ‘research modes’ with expanded stimulation capabilities that might be unlocked in appropriate Investigational Device Exemption (IDE)/IRB controlled trials. Investigators should work closely with manufacturers in planning and executing mapping studies in order to make effective use of these additional features. There are a number of approaches to address the goal of functional mapping in response to electrical stimulation. In peripheral nerve stimulation studies, the desired nerve or branch can be identified anatomically and the range of responses confirmed directly by performing a stimulus response assessment [45]. However, this is not sufficient for addressing the more complex circuits of the spinal cord targeted here. In clinical deep brain stimulation, for example, the implanted electrodes can be exteriorized by attachment of the leads to temporary percutaneous extensions so that the leads can be safely connected to external stimulation or recording equipment. In some centers, this has allowed a period of hours to a several days for measuring responses, testing specific research hypotheses and optimizing parameters [46–47]. In this approach, the stimulation leads remain stationary, the percutaneous extensions are removed post parameter optimization and the original leads are connected to an implantable clinical stimulator. A similar approach is often used for

screening patients as candidates for SCS therapy for chronic pain, where a percutaneous lead is used to confirm responsiveness and general location of placement, and then this is removed and replaced with a permanent pain control stimulator [48]. Though yet untested, this approach might be considered for parameter optimization in epidural stimulation as a treatment for SCI. As is the case whenever there are external leads from the body, consideration of infection must be taken into account with fastidious care followed to avoid this potential complication. Here is also where the experience and best practices of the DBS and chronic pain management researchers and clinicians should be used to minimize this risk. Finally, while a temporary lead might be used to answer scientific questions, it is possible that upon removal and replacement with a permanent stimulator, slight changes in the location of the electrode would require repeating the initial location mapping process to obtain the necessary precision for control of the targeted circuitries. As better technology and imaging procedures are developed, a more precise procedure may be developed. In the interim, this proposed approach to SCS mapping appears to warrant consideration as a practical means to determine the most effective stimulation parameters for a given patient.

Section V Participant Selection and Length of Follow-up

Participant selection should be specific to the hypotheses under study. When the hypothesis, for example, is that SCI individuals will experience improved bladder capacity after stimulation, researchers should include participants who are most likely to exhibit change (e.g. those with small bladder capacity measured during repeated baseline sessions).

Other recommendations for participant selection include:

- Participants should be at least two years out from their injury with a substantial degree of health stability
- No major co-morbidities including cancer, diabetes, heart disease, or stroke
- Participants should be willing and able to return for repeated follow-up studies as required to assess functional and health status
- Participants should not be excluded based on their use of urinary catheters
- Include both men and women

Studies using epidural spinal stimulation in individuals with SCI have so far only included men. Women, however, make up 20 percent of all persons with SCI (2013, National Spinal Cord Injury Cord Injury Statistical Center). Due to a scarcity of research and the need to understand the differences, if any, in the response to epidural stimulation, these early feasibility studies should include both males and females. A 1998 study found differences between men and women in cause of injury, use of medications, attendants, transportation, and type of insurance. However they also found "more similarities than differences in the ways in which they manage life with SCI." [49]. For a full spectrum of understanding and technique translation to diverse populations, it is also important to recruit under-represented minority populations to prospective studies.

Issues related to length of follow-up require careful consideration. Stimulation can have a nearly immediate impact on function. If an immediate effect is seen, follow-up will be needed to determine whether the effect persists and whether it grows stronger or weaker with time. Estimates of the time course of immediate effects will be needed to plan appropriate follow-up. It is possible that some effects of stimulation may only emerge after stimulation has been used for a long duration. This should be taken into consideration when determining the length of follow-up, as the study time should match the time course of the apparent effect.

There is also the possibility that after completing a study, subjects will choose to keep their stimulators implanted and continue to use them in daily life. The study protocol and informed consent document should address specific plans for long-term follow-up and maintenance of the spinal stimulation device. For the long-term, it has been suggested that the researcher and his or her institution evaluate the participant every six months. After completion of the study, the removal of the device is dependent on several criteria: the device is no longer serving the best interests of the participant or the participant requests removal of the device. If the participant decides to continue with the implanted medical device, this should involve consideration of long-term resource allocation. Initiation of an invasive device study includes an obligation of the investigators to support the participant's follow-up.

Section VI Safety and Anticipated Adverse Events

All human subject studies should be designed and performed under close supervision by an appropriate data and safety monitoring board comprised of individuals who are not directly involved in the research. With regard to general safety of participants in the lab and at home during the study, each participant will likely differ in terms of when they can be sent home with the stimulator. Researchers at the University of Louisville have developed a checklist that includes criteria about "readiness" of the participant to function independently outside the lab after training. When a participant is sent home, programs (range of settings) for the stimulator are limited so that the greatest degree of safety is assured for each participant. To protect the health and safety of the participant, it is essential that investigators work closely with device manufacturers, Food and Drug Administration (FDA) reviewers, and the institutional IRB.

Given the long-term goal of providing bladder control without medication, it is recommended that interventions are conducted with and without medication for bladder control. However, patient safety should be thoroughly considered before taking patients off any medications.

The FDA has provided a list of potential adverse outcomes for commercial epidural stimulators in patients seeking relief from pain of trunk and limbs. The key potential adverse events include: (1) skin breakdown or infections at the site of the stimulator implant; (2) epidural hemorrhage, hematoma, infection, spinal cord compression or paralysis from placement of a lead in the epidural space; (3) increased number of infections, constipation, changes in voiding function; (4) undesirable changes in stimulation, which may be related to

cellular changes in tissue around the electrodes, changes in electrode position, loose electrical connections, or lead failure; (5) cerebral fluid leakage; (6) stimulation in unwanted places; (7) paralysis, weakness, clumsiness, numbness, or pain below the level of the implant; (8) persistent pain at the electrode or implantable pulse generator system (IPG)site; (9) seroma (mass or swelling) at the IPG site; (10) allergic or rejection response to implant materials, implant migration or skin erosion around the implant; (10) autonomic dysreflexia; (11) hypotension; (12) hypertension; (13) bladder storage issues; (14) bladder distension; and (15) and battery failure.

It is also recommended that blood pressure monitors be used during stimulation to check for autonomic dysreflexia at the lab and when the participant is at home. Researchers are also urged to monitor kidney function and perform renal ultrasound every six or seven months until measurements are stable. Renal function should be monitored thereafter on an annual basis.

The initial studies are aimed at stimulation mapping to identify parameters that can produce a notable change in bladder, bowel, or sexual function without any adverse effects. These initial studies will objectively determine the effectiveness of any stimulation parameters with resultant functional changes and will provide some measure of the variability in change as well as variability in the choice of effective stimulation parameters. With improved bladder, bowel, and sexual function as primary outcomes for the initial study, it is reasonable to consider what might be the minimal level of change that would be significant for the participant. It is recognized that the cost-benefit balance for changes in measures such as bladder capacity may be patient-specific. The recently published FDA draft guidance on Patient Preference Information may be useful in helping clarify a ‘successful’ outcome for a specific patient: [http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM446680.pdf]. In any event, outcomes for a definitive clinical trial will need to be defined after these initial mapping studies are complete.

Section VII Summary of Future Research Considerations

Since the results of applying SCS to persons with SCI were reported in 2014, the researchers and NIBIB have received numerous e-mails from persons with paralysis and their family members. These have passionately requested information about SCS and how they too can become research participants. Dr. Roderic Pettigrew, Director of NIBIB, stated in the RWJF Human Capital Blog in September 15, 2015, “With such promising results from a technology that is already making a huge difference in several patients’ lives, there is an urgent need to develop the spinal stimulation technology so that it can be quickly and safely adopted by others.” The goal, therefore, is to determine the utility and safety of SCS in a large population of persons with SCI so that this new technology may be made available to all persons with SCI whom it might benefit.

Although there is a high level of enthusiasm for developing epidural stimulation as an intervention for people with SCI, there is also recognition that the mechanism(s) of action are not fully understood and that procedures for determining effective stimulation

parameters in terms of the stimulation site, intensity, rate, and schedule need to be well developed. In regard to planning future epidural stimulation studies, it was suggested that stimulation mapping should be conducted before testing SCS for persons with SCI in a large clinical trial study. This would help address the pressing need for more information about the optimal sites for stimulation, the optimal patterns for stimulation, the ways to develop stimulation parameter space mapping efficiently for a specific individual, and the time course of the changes. While it is probable that animal studies can help clarify the basic principles that underlie functional recovery and give insight on effective parameters, there was general agreement that this eventually must be demonstrated in humans. The details, however, of how to best approach stimulation space mapping are challenging. The potential stimulation matrix of parameters and locations is large and the time periods for many of the effects are long. The best chance of realizing an effective outcome with spinal cord stimulation is to encourage a concerted, transdisciplinary approach that utilizes scientific knowledge of the anatomy and physiology of the relevant systems, and evidence based assessments of responsiveness to stimulation paradigms. For generalized application, there is a need to develop algorithms to systematically optimize the selection criteria for effective electrical epidural stimulation.

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Appendices

Appendix A: Proposed Research Study Hypotheses

The following proposed research study hypotheses would be focused on evaluating the safety of the intervention and on examination of outcome measures of bladder, bowel, and sexual function and patient reported quality of life. For the purposes of this framework, appropriate stimulation refers to the stimulation parameters optimized for the given biological effect.

Overall

Hypothesis #1 Spinal epidural stimulation is not associated with increased adverse events in the chronically injured SCI individual

Hypothesis #2 Spinal epidural stimulation is associated with increased urinary, bowel, or sexual function

Hypothesis #3 Use of epidural stimulation provides a measurable improvement in patient reported health-related quality of life

Hypothesis #4 Spinal epidural stimulation results in fewer episodes of autonomic dysreflexia (AD) related to bladder, bowel, or sexual activity for those individuals who experience AD on a regular basis

Bladder

Hypothesis #5 Bladder capacity is increased with appropriate epidural stimulation

Hypothesis #6 External urethral sphincter activity is increased during bladder filling with epidural stimulation

Hypothesis #7 Appropriate epidural stimulation improves coordination between the detrusor muscle and external urethral sphincter muscles [http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3365101/]

Hypothesis #8 The volume of residual urine is decreased after voiding with epidural stimulation relative to voiding without stimulation

Hypothesis #9 The time it takes to completely void is reduced with epidural stimulation

Hypothesis #10 Voiding with epidural stimulation reduces the dependence on clean intermittent catheterization, the incidence of upper and lower urinary tract infections, and related hospitalization

Bowel

Hypothesis #11 Epidural stimulation decreases total time devoted to a bowel care program

Hypothesis #12 Epidural stimulation decreases episodes of incontinence

Hypothesis #13 Epidural stimulation improves the regularity of bowel movements

Hypothesis #14 Epidural stimulation decreases the need for bowel medications, suppositories, and/enemas

Hypothesis #15 Epidural stimulation decreases the need for manual maneuvers performed digitally and/or with assistive/adaptive devices

Hypothesis #16 Anorectal manometry and/or defecography measures improve with epidural stimulation (direction of improvement may reflect reflexic vs. areflexic bowel)

Sexual function

Hypothesis #17 Epidural stimulation for persons with SCI improves their ability to achieve sexual arousal and sexual satisfaction

Appendix B: Consortium Members

Dawn Bardot, PhD, Senior Program Manager, Medical Device Innovation Consortium; Michael Boninger, MD, Medical Director, Physical Medicine and Rehabilitation, University of Pittsburgh; David Borton, PhD, Assistant Professor of Engineering, Brown University; Anne Pelletier Cameron, MD, Department of Urology, University of Michigan; Alison Cernich, PhD, Director National Center for Medical Rehabilitation Research/NICHD/NIH; Graham Creasey, MD, Paralyzed Veterans of America Professor of Spinal Cord Injury Medicine, Stanford University School of Medicine; William de Groat, PhD, School of Medicine, University of Pittsburgh; Timothy Denison, PhD, Engineering Director, Medtronic. Inc.; V. Reggie Edgerton, PhD, Integrative Biology and Physiology, University of California at Los Angeles; John C. Gore, PhD, School of Medicine, Vanderbilt University; Kenneth J. Gustafson, PhD, Center for Neural Engineering, Case Western Reserve University; Warren Grill, PhD, Biomedical Engineering, Duke University; Suzanne L. Groah, MD, Medstar National Rehab Network, Washington, DC; Susan Harkema, PhD, Rehabilitation Research Director, University of Louisville; Susan P. Howley, Executive Vice President for Research, The Christopher & Dana Reeve Paralysis Foundation; Charles Hubscher, PhD, Director of Graduate Studies, University of Louisville School of Medicine; John Hughes, Chairman, Board, The Christopher and Dana Reeve Foundation; Lyn Jakeman, PhD, Program Director Spinal Cord Injury Research, National Institute of Neurological Disorders and Stroke/NIH; Robert S. Keynton, PhD, Department Chair Bioengineering, University of Louisville; Naomi Kleitman, PhD, Vice President for Research, Craig H. Neilsen Foundation; Kip Ludwig, PhD, Program Director Neural Engineering, National Institute of Neurological Disorders and Stroke/NIH; Michael Moffitt, PhD, Director, Neuromodulation Research and Advanced Concepts, Boston Scientific; Gregory F. Molnar, PhD, Director Neuromodulation Research, Medtronic, Inc.; Vivian K. Mushahwar, PhD, Professor, Division of Physical Medicine & Rehabilitation, Department of Medicine, University of Alberta; Joel Myklebust, PhD, Center for Devices and Radiological Health, Food and Drug Administration; Lanitia Ness, Clinical Systems Engineer, St. Jude Medical, Inc.; Louis Quatrano, PhD, National Center for Medical Rehabilitation Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development/NIH; Nico Rijkhof, PhD, Professor, Faculty of Medicine, Aalborg University; Nicholas Terrafranca, Jr., DPM, Chief Executive Officer and Co-Founder, NeuroRecovery Technologies, Inc.; Louis Vera-Portocarrero, PhD, Senior Scientist Neuromodulation Research, Medtronic, Inc.; Ruth Voor, President & CEO, Vivorte, Inc.; Douglas Weber, PhD, Program Manager Biological Technologies Office, Defense Advanced Research Projects Agency; Peter Wilderotter, President & CEO, The Christopher & Dana Reeve Foundation.

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Biographies

Roderic I. Pettigrew, Ph.D., M.D., is Director of the National Institute of Biomedical Imaging and Bioengineering (NIBIB) at the NIH. From 2013–2014, the NIH Director appointed Dr. Pettigrew as the Acting Chief Officer for Scientific Workforce Diversity to establish program oversight of all NIH activities that address the unique diversity and inclusion challenges, to strengthen the national biomedical research workforce. Prior to his appointment at the NIH, Dr. Pettigrew was Professor of Radiology, Medicine (Cardiology) at Emory University in Atlanta, Georgia, Professor of Bioengineering at the Georgia Institute of Technology, and Director of the Emory Center for MR Research at the Emory University School of Medicine. He is known internationally for his pioneering work at Emory University involving four-dimensional imaging of the cardiovascular system using magnetic resonance (MRI). His current research focuses on integrated imaging and predictive biomechanical modeling of coronary atherosclerotic disease.

William J. Heetderks is Vice-Chair, Trans-NIH FDA Medical Devices Research Interest Group (former Chair from 2013 – 2015); his interest in medical devices research spans a number of decades. Several years ago in the NINDS, he was very involved in development in implantable medical devices for restoration of neurological function such as the cochlear implant, visual prosthesis, brain computer interface, and functional electrical stimulation of spinal cord injured individuals. Formerly as director of the extramural program at NIBIB he had the overview on a broad range of imaging and medical devices with a particular interest in point-of-care diagnostics and therapeutics, and mobile health. Currently his new role is

Clinical Deputy Director, Division of Neurological and Physical Medicine Devices, Office of Device Evaluation, Center for Devices and Radiological Health, Food and Drug Administration.

Christine A. Kelley is the Director of the Division of Discovery Science and Technology and the Acting Associate Director for Extramural Science Programs at the NIBIB. She received her Ph.D. degree in Cell Biology from Boston University in 1988. Her graduate research focused on the role of pericytes in the microvasculature. From 1988–1996 Dr. Kelley conducted postdoctoral and independent research on the function and regulation of smooth muscle and nonmuscle myosin isoforms in the Laboratory of Molecular Cardiology in the National Heart, Lung, and Blood Institute (NHLBI). In 1996 Dr. Kelley became a Health Scientist Administrator in the Vascular Biology Research Group within the Division of Heart and Vascular Diseases in the NHLBI, before moving in 1998 to a position as a Health Scientist Administrator in the Bioengineering and Genomic Applications Research Group within the same Division. Dr. Kelley assumed her current position in NIBIB in March 2002.

Grace C.Y. Peng received the B.S. degree in electrical engineering from the University of Illinois at Urbana, the M.S. and Ph.D. degrees in biomedical engineering from Northwestern University. She performed postdoctoral and faculty research in the department of Neurology at the Johns Hopkins University. In 2000 she became the Clare Boothe Luce professor of biomedical engineering at the Catholic University of America. Since 2002, Dr. Peng has been a Program Director in the National Institute of Biomedical Imaging and Bioengineering (NIBIB), at the National Institutes of Health. Her program areas at the NIBIB include mathematical modeling, simulation and analysis methods, and next generation engineering systems for rehabilitation and neuroengineering. Since 2003, Dr. Peng has chaired the Interagency Modeling and Analysis Group (IMAG), which facilitates the activities of the Multiscale Modeling (MSM) Consortium. Dr. Peng is interested in promoting the development of intelligent tools and reusable models, and integrating these approaches in engineering systems and multiscale physiological problems.

Steve Krosnick received his bachelor's degree from the University of Pennsylvania and his M.D. from Tufts University School of Medicine. He continued training in the Tufts University system for diagnostic radiology and radiation oncology, with board certification in both. He has served as a medical officer at NIH for nearly 15 years, most recently at NIBIB.

Katharine D. Egan is the Director, Office of Science Policy and Communications at the NIBIB. She manages a team of science writers, media specialists and multimedia producers to translate NIBIB research advances into health information for dissemination to the media, Congress, health practitioners, scientists, and other stakeholders. Prior to joining NIBIB in 2012, she was Communications Director at a sister institute, the National Institute of Mental Health, where she worked for nine years in both policy and communications. She has also held writing and public affairs positions at the American Cancer Society, the Yerkes Primate Center at Emory University and the Winship Cancer Center, also at Emory. Additionally, she has worked in communications at the Centers for Disease Control and Prevention (Division of Cancer Prevention), Georgetown University Medical Center, and WETA–TV.

Lyn B. Jakeman is a Program Director providing oversight for extramural research on spinal cord injury and regeneration at the National Institute of Neurological Disorders and Stroke (NINDS). She earned a Ph.D. in Neuroscience from the University of Florida, did postdoctoral training in Neuroscience and Endocrinology at Genentech, Inc., and was a Staff Scientist at the Institute of Pharmacology at Syntex Research (Biosciences) in Palo Alto, California. From 1995–2013, she was on the faculty in the Department of Physiology and Cell Biology at the Ohio State University, where she maintained an active research

laboratory studying the role of glial cells and the extracellular matrix in recovery after spinal cord injury in rodent models.

Michael Marge is Scientific Advisor and Professional Consultant to the Division of Extramural Sciences, National Institute of Biomedical Imaging and Bioengineering (NIBIB). He is a behavioral scientist with a specialization in child psychology, speech-language pathology and audiology and the prevention of secondary conditions in individuals with disabilities. He received his doctorate at Harvard University followed by postdoctoral studies at Columbia University, where he specialized in the diagnosis and treatment of individuals with neuropathologies Dr. Marge served as Deputy Associate Secretary for Planning, Research, and Evaluation, US Office of Education/U.S. Department of Health, Education & Welfare (DHEW); Deputy Director of International Programs, US Office of Education/DHEW; Dean and Professor of Communication Sciences and Disorders, Syracuse University; Founder and Director of the Syracuse University Center on the Prevention of Disabilities; Deputy Director, Office on Disability, Office of the Secretary/U.S. Department of Health and Human Services (HHS); and scientific advisor and professional consultant to the Brookings Institution, Foundation of the National Institutes of Health (NIH), Social Security Administration, Centers for Disease Control and Prevention, National Institute of Child Health and Human Development, National Center for Medical Rehabilitation Research/NIH, and numerous other health related organizations and institutions.

Table 1

Baseline measures and information to be obtained before implantation

Recommended Measures and Information:	
1	MRI imaging of the cord lesion, possibly fMRI of resting circuitry;
2	Spinal cord conduction to evaluate completeness of lesion, e.g. somatosensory evoked potentials, motor evoked potentials, etc.;
3	Bladder tests to include urodynamics (filling cystometry and pressure flow studies including EMG documenting bladder compliance; involuntary and voluntary bladder contractions; and rhabdosphincter (or ‘external urethral sphincter’) contraction and relaxation; bladder capacity; volume voided; post-void residual volume; and sensation during filling);
4	Use of a three-day bladder (catheterization and/or voiding) diary to document incontinence episodes, volume voided, frequency of voiding; obtain neurogenic bladder symptom score [29];
5	Cardiovascular function in preparation for studying conditions such as autonomic dysreflexia and postural hypotension; also blood pressure and autonomic dysreflexia monitoring during epidural stimulation in the lab;
6	Medications being used that may affect the bladder, bowel, and sexual function;
7	Bladder management, including information about use of catheterization;
8	Bowel diary, indicating fecal continence, dates and times of defecation and duration of bowel emptying activity and medications affecting bowel; obtain colonic transit time; obtain the bowel dysfunction score [30]; also see http://www.ncbi.nlm.nih.gov/pubmed/18725887;
9	Sexual function questionnaire and erectile response to vibratory stimulation of penis or sacral segments. See http://www.ncbi.nlm.nih.gov/pubmed/21283085 and http://www.ncbi.nlm.nih.gov/pubmed/21383760, [31–33].