Explanation of the CME Activity

CME EXPLANATION OF THE CME ACTIVITY.

CME Monograph

Kristjan T. Ragnarsson, MD; Lisa-Ann Wuermser, MD; Diana D. Cardenas, MD, MHA; Ralph J. Marino, MD, MSCE

Post-Test

CME Questions for CME Credit.

Evaluation Form


EXPLANATION OF THE CME ACTIVITY

TARGET AUDIENCE
This activity is intended for physiatrists who treat patients with spinal cord injury (SCI).

STATEMENT OF NEED
Currently, there is no cure for SCI. However, new research strategies are being developed to help promote recovery and contribute to functional improvement for patients with acute, subacute, and chronic injuries. New surgical procedures, pharmacologic treatments, and functional neuromuscular stimulation methods are evolving due to well-controlled, objective trials that assess a patient’s neurologic and motor functional improvement from therapy. Although there are other important types of functional recovery that are relevant to patients with SCI, such as bowel, bladder, respiratory, and skin integrity, this monograph specifically focuses on the area of neurologic and motor functional recovery, a significant scope to thoroughly cover by itself.

Physiatrists play an essential role in evaluating the value of proposed clinical trials and in recruiting patients for enrollment. To facilitate the development of SCI clinical trials, this monograph intends to detail the implementation of clinical trials, describe the research in SCI rehabilitation currently being pursued, and provide a critical analysis of study objectives and measurement tools that are available to assess an intervention’s outcome. This monograph will be most useful as background information for physiatrists new to trial development in the field of physical medicine and rehabilitation, who intend to participate in multi-center clinical trials with predesigned protocols. The rehabilitation community will benefit from an awareness of the issues associated with the performance of current clinical trials in SCI, from a compendium of resources toward clinical trial development, and from a description of the archetypical characteristics of a clinical trial in SCI.

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Learning Objectives
On completion of this activity, participants should be better able to:

- Discuss the role of the physiatrist in participating in, recruiting patients for, and evaluating SCI clinical trial (primarily multicenter, randomized, controlled trial) objectives and outcomes.
- Explain issues in SCI research protocols design and evaluation.
- Describe trends that may be expected to have an effect on the future of rehabilitation medicine in clinical practice.
- Describe the key multicenter and other major clinical trials currently under way for chronic SCI interventions aimed at improving functional status.
- Describe the primary outcome measures being utilized for evaluating functional status.

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INTRODUCTION
Kristjan T. Ragnarsson, MD
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Diana D. Cardenas, MD, MHA
Ralph J. Marino, MD, MSCE

In the United States, there are an estimated 11,000 new cases of spinal cord injuries (SCIs) each year.1 Approximately 250,000 people are alive in the United States who have had an SCI.1 Primarily, SCI is caused by motor vehicle crashes (50.4%), falls (23.8%), acts of violence (11.2%), and sports (9.0%). SCI most commonly affects young, working-age adults,1 80% of whom are men.1 The average age of injury has been gradually increasing, and for persons injured since 2000, it is reported to be 38.0 yrs. At the time of injury, 63.0% are employed, but 10 yrs after the injury, 68.3% of persons with paraplegia and 73.3% of persons with tetraplegia are still unemployed. Such high unemployment clearly contributes to the financial burden of SCI on society, through lost wages, fringe benefits, and productivity,1 although the exact cost of unemployment is incalculable due to variations in education, employment status, and income. In contrast, it has been estimated that during the first year after SCI, the average cost of healthcare and living expenses alone for a person with high tetraplegia (C1–C4) is $682,957 and $249,549 for persons with paraplegia.1 The cumulative lifetime costs of care for persons with tetraplegia and paraplegia arguably have increased as medical care has improved and resulted in their increased life expectancies. Historically, renal failure was the most common cause of death after SCI, but advances in urologic management have shifted the leading causes of mortality to pneumonia, pulmonary emboli, and septicemia.1

SCI can be described according to the neurologic level and the severity of impairment. The skeletal level (i.e., the site of greatest vertebral damage according to the radiographic examination) is of lesser importance. The optimal method to clinically assess neurologic impairment after SCI is by performing a neurologic examination of the patient—who should be in the supine position—and documenting the findings according to the International Standards for
Neurological Classification of Spinal Cord Injury.\(^2\)\(^,\)\(^3\) Testing of certain key muscles provides a total motor score (Table 1), and testing of all neurologic sensory segments below C1—for light touch and pinprick—provides a total score for these two key sensory modalities (Fig. 1). This allows the examiner to determine the exact sensory and motor levels of the SCI and whether the injury is neurologically complete or incomplete. The neurologic level is defined as the most caudal segment of the spinal cord with normal sensory and motor function on both sides of the body. The term tetraplegia is used to describe SCI with impaired neurologic function in the cervical segments of the spinal cord, whereas the term paraplegia refers to SCI in the thoracic, lumbar, or sacral portions of the spinal cord. Complete SCI is defined as no sensory or motor function preserved in the lowest sacral segments (S4–S5), whereas incomplete injury has partial preservation of sensory or motor functions below the neurologic level and includes the lowest sacral segment. The various degrees of neurologic impairment are classified according to the American Spinal Injury Association (ASIA) Impairment Scale (AIS) (Table 2), which is a modified form of the older Frankel Scale. Persons with complete SCI often have innervation of dermatomes and myotomes below the lowest normal neurologic segment. This area is referred to as the zone of partial preservation. Some clinicians still describe neurologic and motor injuries using the various clinical syndromes of SCI (e.g., central cord, Brown Sequard, anterior cord, conus medullaris, and cauda equina syndromes), terms that are retained in the Standards despite their imprecise meaning.

Using the International Standards, the most frequent neurologic categories are incomplete tetraplegia (29.5%), complete paraplegia (27.9%), incomplete paraplegia (49.2%), and complete tetraplegia (30.8%).

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<th>TABLE 1 Medical Research Council scale of muscle strengths</th>
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FIGURE 1 Standard neurologic classification of spinal cord injury.
complete paraplegia (21.3%), and complete paraplegia (18.5%).\textsuperscript{1} Although prognosis for neurologically complete SCI remains grave, it has been shown that as many as 30–80% of persons with complete tetraplegia regain one motor level within 1 yr of SCI and that as many as 10–15% of patients initially designated as ASIA A improve by at least one ASIA impairment grade, thus converting from complete to incomplete SCI.\textsuperscript{4} This conversion may be due in part to an initial grade misclassification, as early neurologic examinations for sedated patients are not as reliable as later neurologic assessments. The potential for incorrect ASIA grade assignment during the early stages after an SCI is worth bearing in mind when treatments for acute SCI are being considered and assessed.

In general, the logical definitions of the International Standards have greatly improved the reliability, consistency, and predictive value of neurologic categorization of persons with SCI. This system is the standard method for SCI evaluation, utilized by almost all major SCI organizations worldwide.

**Evidence-based Medicine for SCI**

During the last 40–50 yrs, there has been a growing need and growing demand to scientifically evaluate different clinical treatments. The field of physical medicine and rehabilitation is no exception. To conduct a clinical trial and evaluate the resulting treatment data, physiatrists need to have a thorough comprehension of the implementation of clinical trials. The comprehensive discussion in this publication of the challenges, design features, and outcome measurements available for SCI trials is aimed to help physiatrists gain a better understanding of conducting clinical trials.

The importance of conducting clinical trials in SCI is underscored by the plethora of resulting benefits obtained from a successful trial. There are many challenges to completing a clinical trial, but the treatment efficacy data procured is the invaluable evidence necessary to substantiate the usage of interventions for SCI. SCI trials create the foundation for the formation of clinical guidelines and standards for proven approaches. Guidelines enable a more uniform approach to SCI interventions, helping to minimize the trend of variability in clinical practices among physicians in different countries and institutions and, sometimes, even within the same institution. In addition, rehabilitation stakeholders, such as healthcare insurance companies, are demanding usage of proven, efficacious methods for persons with SCI.\textsuperscript{5} In general, the development of scientific, evidence-based interventions predictably reduces the rate of inappropriate care formulated from singular observations or opinions, which sometimes have iatrogenic outcomes.

Two recent publications have highlighted the need for stronger scientific foundations for treatments of persons with disability. In 2003, John Whyte,\textsuperscript{6} of the Moss Rehabilitation Center in Philadelphia, wrote, "Across rehabilitation, there is a shortage of treatments that have demonstrated efficacy and effectiveness through rigorously controlled clinical trials" in his opening statement on a discussion of obstacles to clinical trials in rehabilitation. The neurologist and Washington University School of Medicine Associate Professor Alexander Dromerick\textsuperscript{7} stated in a recent guest editorial, "Along with much of psychiatry and complementary therapies, the field of rehabilitation lacks the solid foundation of empirically derived data demonstrating the efficacy of key interventions." Over the course of their disease intervention, patients with SCI typically undergo an integrated regimen that may include pharmacologic interventions, surgical therapies—such as with most treatments aimed at regeneration\textsuperscript{8}—and most commonly, various rehabilitative treatments.\textsuperscript{9} Rehabilitation interventions are the key components to improving the quality of life of persons with SCI, and should be supported by the same, rigorous methods that help define a pharmacologic or surgical therapy. However, there are several reasons why rehabilitative interventions for SCI have historically been rendered without scientific evidence of efficacy. Rehabilitative interventions for SCI generally make

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<th>Table 2</th>
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<tr>
<td>A</td>
<td>Complete No sensory or motor function is preserved in the sacral segments S4-S5.</td>
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<tr>
<td>B</td>
<td>Incomplete Sensory, but not motor function, is preserved below the neurological level and includes the sacral segments S4-S5.</td>
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<tr>
<td>C</td>
<td>Incomplete Motor function is preserved below the neurological level, and more than half of key muscles below the neurological level have a muscle grade of &lt;3.</td>
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<tr>
<td>D</td>
<td>Incomplete Motor function is preserved below the neurological level, and at least half of key muscles below the neurological level have a muscle grade of ≥3.</td>
</tr>
<tr>
<td>E</td>
<td>Normal Motor and sensory function are normal.</td>
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sense and are safe. In essence, these qualities lower the attention and thereby criticism directed at SCI interventions. Second, rehabilitation medicine clinicians often endeavor to promote functional independence and quality of life—goals that have less easily demonstrable endpoints than measurements of survival, morbidity, and changes in laboratory values. Inherently, soft endpoints make designing methodologies and standardizing interventions difficult. Finally, there is a much smaller amount of money dedicated to the development of rehabilitation interventions—relative to the sum of money driving the refinement of drug treatments—simply because the commercial earning potential of rehabilitative therapies is small.

**Historical Overview of SCI Clinical Trials**

Clinical trials research in SCI was revolutionized by the National Acute Spinal Cord Injury Study (NASCIS). In 1984, the first NASCIS trial, an investigation of methylprednisolone sodium succinate, was published and established a new precedent of scientific rigor in SCI research. The landmark study became the standard for conducting clinical trials in SCI, from the usage of neurologic change scores to the evaluation of both motor and sensory impairment. Although the NASCIS I trial failed to show a difference between the control and experimental groups, its true significance lies in the fact that it was the first large, multicenter, randomized, controlled trial in SCI.

The NASCIS II trial had a similar experimental design, but it evaluated the neurologic outcomes of patients treated with either methylprednisolone sodium succinate, naloxone, or placebo. The study, published in the *New England Journal of Medicine* in 1990, was another landmark event for SCI research. It was the first randomized, double-blind, placebo-controlled interventional SCI trial that reported a positive treatment effect on neurologic recovery.

Promising pilot data for the ganglioside, GM-1, led to the Sygen Multicenter Acute Spinal Cord Injury Study. This study involved 797 patients and 28 centers in North America, making it the largest clinical trial ever conducted for an SCI intervention. It, too, was a randomized, double-blind, placebo-controlled trial, and although it failed to conclusively demonstrate efficacy, the study, along with the NASCIS trials, helped to establish a new gold standard for conducting SCI trials. These studies also helped to establish protocols that have become the standard of care in SCI, and quite significantly, the trials strongly suggested that the basis for SCI interventions should be rigorously controlled scientific evidence.

In an effort to promote further studies in SCI that maintain the standard established in the NASCIS and Sygen Multicenter Acute Spinal Cord Injury Study trials, this publication details the issues that are unique to SCI trials, the methods to overcome challenges in conducting an SCI trial, optimal study designs for SCI, current SCI clinical trials, and the outcome measures that are available and tailored for SCI. Rehabilitative interventions for SCI, in particular, have had a surge of progress, as assistive technology has been advanced by recent bioengineering research and the establishment of pioneering assistive technology companies within the past 5 yrs.

**AMELIORATING THE CHALLENGES OF SCI TRIALS**

**Lisa-Ann Wuermser, MD**

Clinical trials are an indispensable means of assessing the efficacy or lack of efficacy of an intervention for SCI. When rigorously conducted, the clinical trial is the only way to safely evaluate potential interventions for the treatment and management of SCI. The goal of an SCI clinical trial is to assess whether a potential therapy is both safe and effective. Accurate data interpretation requires that the clinical trial be conducted in a methodical, rigorous manner, with careful attention to consistency in both delivery of the intervention and evaluation of the outcome. However, the circumstances of SCI often create confounding variables that make intervention administration and result interpretation complicated. Obstacles for SCI trials can include enrolling an adequate number of patients, negotiating transportation for treatment and follow-up, establishing treatment norms—particularly for rehabilitative therapies, with multiple locations, providers, and time points—and identifying appropriate outcome measurements. Furthermore, complex interventions can be difficult to administer in a standardized fashion. Many of these variables can be minimized by carefully designed and clearly written protocols, well-trained staff, compulsive documentation, routine use of standard operating procedures, and monitoring and auditing of studies.

**Recruitment and Retention of Subjects**

Successful recruitment and retention of research subjects is vital to any clinical trial. In acute SCI, the primary barrier is the confusion surrounding the event itself. Patients often express interest in participation in a clinical trial, particularly with the hope of receiving an intervention that may improve their functional or neurologic outcome. However, with only about 11,000 new SCI cases per year in the United States, there is a limited pool from which to draw subjects. Most clinical trials focus on specific levels of injury or AIS classifications, and all have clear inclusion and exclusion criteria.
criteria. Also, most do not include the older patients in their trials, despite recent data that >10% of new injuries are sustained by persons over the age of 60. Therefore, demographic issues alone may reduce the pool to less than half of all new injuries each year.

Recruiting individuals with chronic SCI for clinical trials is generally an easier task. With roughly 250,000 people living with SCI within the United States who have SCI with a variety of neurologic levels and degrees of injury completeness, there is often an adequate pool of SCI patients for clinical studies, particularly if the expected result is robust. The potential participants have achieved neurologic and functional stability, minimizing the variability of possible outcomes, thus making the measurement tools easier to select. However, recruitment suffers from issues of advertising and access, particularly in light of the Health Insurance Portability and Accountability Act of 1996 (HIPAA) requirements. It can be useful for clinical trial centers to maintain an Institutional Review Board–approved registry of persons with SCI who have agreed to be contacted for participation in clinical trials. A registry allows the principal investigator to query the database and obtain a list of people interested in clinical trials with the specific demographic characteristics that are necessary for the study. Registries are not difficult to develop or maintain, but they must stay current and be Institutional Review Board approved. Patients may be approached for participation in a trial while being seen for an outpatient visit. The patient is asked to sign a simple consent form that states willingness to be in the registry and to declare some basic information to be contained within the registry database. Once constructed, it is an invaluable resource. Without it, investigators must attempt to recall appropriate patients or wait until patients come in spontaneously. Patients of other physicians can only be approached if their own physician asks them to consider participating in the study and then have signed a small form documenting their interest, allowing study personnel to contact them. Although this last technique seems easy, the added layer requires extra time and effort to already rushed clinical visits. It may be advisable for clinicians seriously interested in directing a clinical trial to initiate a registry. In the past, large databases of patients were mined for potential clinical trial subjects. However, unless the consent form specifically states willingness to be contacted for clinical trials, these methods can no longer be used to identify subjects.

Adequately Powering a Clinical Trial

Any well-designed trial is developed using a power study to determine the number of subjects needed. A power study takes into consideration the expected effect of the intervention on the primary outcome measure and the variability of that outcome measure among those with no intervention, and then calculates the number of subjects needed to detect a real difference between the groups—a difference that is unlikely to have occurred by chance alone. If the size of the effect is small, then the number of subjects needed to detect a difference becomes quite large. If the variability of outcomes is great, then again a large number of subjects will be needed to overcome the possibility that the differences noted occurred by chance alone. The outcomes measured, the homogeneity of the population, the predictability of the outcomes, and the size of the effects all influence the likelihood of detecting the effect of intervention. With the variability of neurologic and functional outcomes among SCI patients and the difficulty of making an accurate, early prediction of who is likely to make a greater recovery, a substantial number of trial participants are needed, even if the effect is expected to be robust. Consequently, people with neurologically complete injuries tend to be better targets for early interventions. Their course of recovery is far more predictable than those with incomplete injuries, even though intuitively, a greater recovery from those already demonstrating incompleteness would be expected.

Study-site Accessibility and Transportation

Acute interventions also require accessibility to the research site to receive the intervention within the designated time window. For example, participants of the activated macrophages trial must be transported to the study site no later than 10 days postinjury. Patients with delays in surgical stabilization or illnesses that prevent transportation to the study site cannot participate. In the NASCIS trials, subjects had to arrive to the emergency department of a study center within 8 hrs of injury. Any delay in extrication or in an outside emergency department delayed participation in the study. These factors can limit the available pool of participants for acute SCI clinical trials.

One cannot speak of the challenges of SCI patient recruitment without discussing transportation. Clinical trials in chronic SCI often require multiple, frequent visits to the study site. Rehabilitative interventions may be performed several times a week, if not daily. For people relying on public transportation for the disabled, or for those who have intermittent personal attendants to manage their transportation needs, this schedule can be very difficult to achieve. For those with acute injuries, the follow-up visits in the hospital are convenient, but the follow-up visits after discharge...
can be very difficult to attend, especially in the early period before accessible vehicles have been obtained. These factors must be considered when designing a clinical trial for people with SCI.

**Informed Consent**

Issues of informed consent and coercion are perhaps the most concerning in this early period. Patients themselves may be too sedated or sick to participate in the consent process, and in some cases, official next of kin may be difficult to find or identify. In the case of research, it is clear that the highest standard of obtaining consent from next of kin must be observed. For example, one cannot obtain consent from a parent if the spouse is competent, even if the parent is more available, unless the patient has a power of attorney designating the parent to speak on his or her behalf. Patients and families also very much want hope, and they look to experimental tests and interventions for that hope. During an National Institutes of Health (NIH)–sponsored study of early indicators of heterotopic ossification, I often had to remind subjects that my study would be of no benefit to them. They would ask me if the tests performed would help me find a way to make them walk. When the intervention is targeting neurologic recovery, it is imperative that the patient understand the experimental nature, the unknown risks, and the likelihood of receiving placebo if that is part of the study design. They must not be allowed to dismiss the risks in an effort to obtain an experimental intervention. The person obtaining the consent has the responsibility to uphold this high standard of informed consent and thus should be trained accordingly. "The Informed Consent Zone" (accessible at: http://www.gregpak.com/iczone/) is an excellent resource for training research staff, and it specifically addresses the issue of coercion and patient misunderstandings of the goals of clinical trials.

**Competition for Study Participants**

For both acute and chronic SCI clinical trials, there is increasing competition for participant enrollment. By 2006, it is likely that there will be at least four clinical trials in acute SCI that will target young people with motor complete SCI in their first 2 wks postinjury. Patients and researchers will be faced with the need to evaluate multiple options to determine which study they will choose to participate in. Participation in one of these four acute-phase trials obviously precludes participation in any other.

The variety of trials of different interventions that address different aspects of the chronic SCI condition confounds the decision process for choosing a study in which to participate. Choosing between studies of bacterial interference treatment to prevent urinary tract infections, robotic-assisted gait restoration (Lokomat® training) to evaluate physiologic responses with different medications, and zoledronic acid to improve bone mass is difficult and forces patients to define a priority list of needs and interests. Although a patient may be eligible to enroll in several trials of this type at a time, the time and effort requirements for participation in multiple trials must be considered.

**Funding a Clinical Trial**

Perhaps the greatest challenge for any clinical trial, and specifically those in SCI, is funding. The overwhelming majority of clinical trials in this country are industry sponsored. It is rare for the NIH or other funding agencies to sponsor a clinical trial due to both funding priorities and the large cost of such trials. Again, the small number of both new injuries and persons living with SCI limit the interest of many large pharmaceutical companies in pursuing therapies for this condition, as the return on the investment is unlikely to change their profit margin. However, a number of corporations, both small and larger, have taken an interest in SCI in the past several years, thereby increasing the number of industry-sponsored SCI trials.

Recent efforts by SCI organizations in the United States have resulted in an increase in funding at the National Center for Medical Rehabilitation Research, the National Institute on Disability and Rehabilitation Research, and the Department of Veterans Affairs Rehabilitation Research and Development Service for multicenter clinical trials in SCI. Already, the NIH has funded a clinical trial consortium for traumatic brain injury, allowing investigators to collaborate on trials of nonpharmacologic interventions or those of older nonpatented medications, which are unlikely to allow a pharmaceutical company to recoup its costs. Although this program is new in its inception and its success is too early to gauge, this model seems warranted in SCI as well.

Foundations and organizations have also taken an interest in this problem. The Christopher Reeve Paralysis Foundation has sponsored the North American Clinical Trials Network, funding five centers in the United States and Canada to set up an infrastructure and database and to define outcome measures for acute SCI interventions (Table 3). The Spinal Cord Injury Committee of the Joint Section on Neurotrauma and Critical Care of the American Association of Neurological Surgeons, the Congress of Neurological Surgeons, and the Joint Section on Spinal Disorders and Peripheral Nerves of the American Association of Neurological Surgeons and Congress of Neurological Surgeons cosponsored the Surgical Treatment for Acute Spi-
nal Cord Injury Study, a multicenter study to determine if very early decompression results in improved neurologic outcomes. Further funding needs remain, however. (Tables 4–6 are resource guides for funding agencies, centers, and programs for SCI research.)

Budgeting is an integral part of establishing a successful research program, yet various budget items may be overlooked by the investigators when a proposal is developed. Funds need to be appropriated into a working budget during the contract negotiation process. Every task that will be performed during a clinical trial should be listed in a line-item list, and fair compensation should be given in the fee for service. Oftentimes, it is easy to underestimate the hidden costs of research, so it is recommended to add 50% to the estimation cost, as the precision of research requires significant time. Filing necessary documentation—including about adverse events and protocol violations—and transporting patients can be surprisingly time consuming.

**Staffing an SCI Clinical Trial**

Once funding and a budget are established, staffing becomes the next hurdle to clinical trial development. It is ideal, of course, to have research staff with experience in the clinical care of persons with SCI. The research staff must be prepared for the transfer needs, occasional bowel or bladder accident, and the identification and treatment of autonomic dysreflexia, should it arise during an intervention. The study area should be equipped for maximum accessibility for the SCI study participants. Research staff must also be trained in clinical trial research methods and impressed with the necessity of rigor for all procedures and testing. At times, outcomes of SCI interventions are not as easily and objectively quantified, for example, as blood pressure or a cholesterol level, although ease of quantification is certainly dependent on the specific outcome measure chosen. Neurologic and functional outcomes are based on examinations and evaluations. Evaluators of outcome must be thoroughly trained to maximize the interrater reliability across the study sites. This task is not impossible, but it requires the commitment of both the research design team and the individual researchers at each study site. The protocols must be followed precisely. The gray area of clinical medicine simply has no place in the documentation of a clinical trial outcome measure.

**CURRENT SCI CLINICAL TRIALS AND THE OPTIMAL STUDY DESIGN**

**Diana D. Cardenas, MD**

**Clinical Trial Designs for SCI Research**

SCI research can vary from neuroregenerative treatments, to pharmacologic interventions, to rehabilitation. All types of SCI research require systematic and thorough designs to promote the collection of data that provides the best evidence of an intervention’s value. The penultimate clinical trial design provides the strongest possible evidence that the observed effects are a direct result of the intervention, rather than due to other influences. Archetypically, this is best achieved by a randomized, controlled, double-blind trial. The circumstances of SCI and the types of interventions that are pursued—especially the rehabilitative—do not lend SCI trials to the archetypical design, although clever alternatives to the paradigm features do enable the creation of an unbiased, objective trial. For example, single-subject designs can work very well and produce useful data. This is especially relevant to cases in which it may be inappropriate to randomize patients, such as with studies of neuroprostheses. Often, there are only small sample sizes available for these studies, and individual variations make randomization unfeasible.

Typically, the crossover design, in which each subject receives both the active and placebo...
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treatments, is considered the optimal scheme for a clinical trial. Drug studies are often designed this way, with a sufficient washout period based on the half-life of the drug and calculations of how long it takes to clear the body. The crossover trial design is not suitable for most SCI studies, however. Trials of extended lengths, and commonly rehabilitative, clinical trials in general, are best designed as a parallel trial (Fig. 2). In this paradigm, a patient is assigned to treatment A or treatment B and continues within that study group for the duration of the trial. Lastly, the open-label trial design produces the least conclusive evidence that an intervention achieves the desired outcome. There is no control group in the open-label trial, and consequently, less evidence is procured that the intervention being studied causes a significant beneficial change in outcome over no intervention.

Double blinding requires that neither the patient nor the investigator is aware of the treatment type. Although SCI pharmaceutical clinical trials can have a double-blinded design, it is not possible to achieve double blinding in rehabilitative SCI trials, as at minimum, patients will be aware of the type of intervention that they are receiving. This knowledge can create the potential for bias according to treatment assignment during the outcome interpretation. However, a successful approach to minimizing bias in SCI trials is to have an independent group of clinicians conduct the outcome measurement. This group may not have contact with the interventionists nor communication about the type of intervention being administered during patient testing.\(^{18}\) Separating the outcome evaluation from the intervention is a clever means for avoiding the bias that can be created by lack of a double-blind design.

Randomization is an essential feature of an objective, well-designed clinical trial and should be used in SCI clinical trials. According to the NIH, clinical trials can be randomized either in a simple, stratified, or a restricted manner. Simple randomization is the assignment of patients to study groups, without restriction, conducted in a manner similar to a flip of a coin (Fig. 2). Stratified randomization involves group assignment defined by patient characteristics, whereas restricted randomization is any procedure applied to achieve balance between study groups in size or baseline characteristics. Randomization minimizes the large variation in response to rehabilitation intervention. Without randomization, the difference in placebo and treatment effect is often a product of underlying patient characteristics, but it may be misinterpreted to be a therapeutic effect.\(^{18}\) In comparison, before/after and other observational design methods do not reliably ablate that subjective influence and can lead to biased interpretations of outcomes.\(^{18}\) Randomization promotes the generation of objective outcome results.

As with randomization, it is feasible to design a controlled SCI study. Including a control markedly increases the quality of the study. This means providing a standard against which the experimental treatment is measured or compared. In pharmacologic SCI trials the comparator can be either an inert placebo or an active placebo. Active placebos mimic some effects of the experimental drug, improving the blindedness of study groups.\(^{23}\) Providing a control group enables a thorough statistical evaluation of the outcome.
Current and Recent SCI Trials

The types of clinical trials vary from the classic trial that assesses a treatment to trials that consider a preventative measure, a diagnostic method, a screening technique, or a quality-of-life investigation. They can be conducted in one of four phases, depending on the number of subjects involved and the purpose, such as studying efficacy, safety, tolerability, dose-ranging, or a new indication (Table 7). Recently completed, published clinical trials were compiled by a search of the National Center for Biotechnology Information PubMed database with the search words "spinal cord injury." Publications between 2004 and 2005 were aggregated in a chart according to the SCI-related condition and type of intervention (Table 8). Furthermore, the following is a compendium of current SCI trials, gleaned from research abstracts, the NIH-sponsored site at www.ClinicalTrials.gov, www.centerwatch.com, or the RehabTrials site (resources are listed in Table 9). The centerwatch.org site lists >41,000 government and industry-sponsored clinical trials and new drug therapies, and the ClinicalTrials site was developed by the National Library of Medicine to provide a regular update of the federally and privately funded clinical research in human volunteers.

An inquiry into the ClinicalTrials database with the search words "spinal cord injuries" indicated 16 current or recently completed medical research trials. Nine of the studies were completed ≥3 yrs previously or were focused on conditions other than SCI; the other seven studies are discussed below. The same query within the CenterWatch clinical trials listing service reported the investigations of four different SCI interventions, two of which were also listed on the NIH site. All the trials that are included below are current SCI trials, conducted with human subjects, with publicly available information. The information is divided between clinical trials for the acute phase of

| Phase I | An exploration trial, conducted with a small group of people (approximately 20–80), to gain early evidence of effectiveness, to evaluate the safety profile, and to identify side effects |
| Phase II | A controlled clinical study conducted with a group of 100–300 people to evaluate an intervention's efficacy, safety, and possible risks |
| Phase III | These trials are expanded controlled and uncontrolled studies conducted after obtaining preliminary evidence of efficacy. The treatment is given to a large group of people (1000–3000), in part, with intent of gathering data for product labeling. Benefit/risk analyses and head-to-head comparisons to other commonly used treatments can be conducted in this phase. |
| Phase IV | A postmarketing study to delineate further information that can include other indications, risks, benefits, and optimal use (such as modifying the dosage or timing of use) for a drug |

Current and Recent SCI Trials

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TABLE 7 Clinical trial phases

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TABLE 8 Results of a PubMed search of 2004–2005 randomized, controlled clinical trials for patients with spinal cord injury

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SCI and for chronic SCI, as the time frames, goals of therapy, and outcome measures used are different.

**Chronic SCI Trials**

**Rehabilitative**

Rehabilitative interventions for SCI may employ bioengineering, computerization, and advanced therapeutic techniques to address functional deficits in ambulation, mobility, and use of the upper extremities. There are several rehabilitative trials currently in progress or that have been recently completed domestically.

The Effects of Sensory Motor Input on Gait in SCI Subjects was a trial designed to assess the improvement of gait for ASIA C-classified SCI patients. The 12-wk efficacy study had a randomized, single-blind, parallel-group design and included 36 patients who were a minimum of 1 yr past their SCI. Two strategies were employed to enhance a treadmill training program: the functional electrical stimulation of a muscle on withdrawal reflex and the addition of body-weight supports for partially suspended patients. Furthermore, a similar study was designed to compare supported ambulation training with conventional gait training for improving gait speed, endurance, efficiency, and muscle function. A total of 40 SCI patients injured >6 mos previously received 12 wks of conventional gait training or supported ambulation training intervention. It was a phase II, randomized, open-label efficacy study. Another rehabilitative trial, the Body Weight Supported Treadmill Training study is currently in progress to assess the gait rehabilitation of SCI patients with an overhead support and harness, compared with conventional therapy. It is a phase I efficacy study, with a randomized, single-blind design.

The CenterWatch Web site listed two other rehabilitative clinical trials that are currently recruiting. First, test methods to improve voluntary walking ability for patients with neurologically incomplete SCI are being assessed in a 13-wk trial. The requirements for participation in the study include SCI of >1 yr duration and voluntary movement in one leg. The study has a randomized, controlled, parallel-group design. Second, a novel intervention for SCI patients with tetraplegia who lack the use of their hands is currently being tested for efficacy. The patient’s thoughts are directly communicated to a computer.

The National Institute on Disability and Rehabilitation Research is sponsoring the largest biomechanics study to date to consider upper limb pain in SCI patients. Three sites will be involved in this collaborative study, involving 200 individuals with paraplegia. The goal of this longitudinal study is to determine the modifiable biomechanical factors present during wheelchair propulsion and transfers that may predict the degree of pathology, clinical findings, and subjective pain in the upper limbs of paraplegics.

A 2-yr clinical trial designed to assess the effects of a holistic health program on SCI patients is reported on the RehabTrials Web site. Patients within the experimental group will attend a series of six workshops, whereas the control group will not. The design is a randomized, controlled clinical trial.

**Pharmacologic**

As noted previously, the precedent for pharmacologic interventions in SCI was set with the publication of the NASCIS trial in 1984. This study published widely accepted results of an improved neurologic outcome for SCI patients treated with methylprednisolone sodium succinate. Current pharmacologic interventions for SCI often are directed at reducing pain. Potentially functionally disabling, chronic neuropathic pain may be induced by SCI. There are several drug studies currently being conducted, or recently completed, to investigate safe and well-tolerated treatments that reduce SCI-induced pain. Furthermore, drug treatments are being pursued for other secondary effects of SCI, including spasticity and heterotopic ossification.

The safety and efficacy of oral 4-aminopyridine for the treatment of SCI-induced spasticity was evaluated in a phase III trial. The randomized, double-blind, placebo-controlled, parallel-group trial had a duration of 12 wks of stable treatment and an enrollment of 204 SCI patients. Patients were required to have a stable condition after their traumatic, incomplete SCI, which must have occurred >18 mos before, and an Ashworth score of >2.0 across four lower limb muscles. A total of 166 patients completed the trial; 78 were in the experimental group, and 88 were in the control group. The Ashworth scores of the 4-aminopyridine group were significantly better than the placebo only at the last measurement taken ($P = 0.006$). 4-aminopyridine is known to increase the nerve conduction of electrical impulses for focally demyelinated axons.

A phase IV study has recently been conducted to evaluate the relief of chronic pain associated with SCI by administration of amitriptyline. A total of 84 participants with >6-mo history of SCI and with >3 mos of associated chronic pain were given either amitriptyline or the active placebo, benztrapine mesylate, for 6 wks. The study design was a randomized, double-blind, parallel-group study to assess the efficacy of the drug. No significant differences were found between groups in
pain intensity or pain-related disability posttreatment, in either intent-to-treat analyses or analyses of those who completed the study.

A recent randomized, double-blind, placebo-controlled crossover trial in 20 patients with paraplegia demonstrated efficacy of gabapentin, an anticonvulsant, in reducing neuropathic pain intensity and frequency.32

A clinical neuropharmacology of pain study in SCI patients is being conducted currently, in Boston.26 The phase IIa clinical trial is designed to assess the safety and tolerability of RGH-896 in patients with <3 mos of persistent neuropathic pain due to SCI.

Lastly, a phase II trial has been completed for HP184, the dual-action sodium and potassium channel blocker for patients with incomplete SCI.33 Safety, tolerability, and pharmacokinetics were studied in a multicenter, randomized, placebo-controlled, double-blind study. Patients with SCI for a minimum of 18 mos and C or D ASIA scale classifications were randomized to the experimental (75%) or the placebo (25%) groups. Patients were sequentially entered into four groups (A, B, C, D) of 12 patients per group and randomized to HP184 or placebo. Groups A, B, and C received oral doses of 100, 200, or 400 mg of HP184 once daily, respectively, or matching placebo on days 1–11. Group D received 400 mg of HP184 once daily on day 1 and day 11 and 400 mg twice daily on day 2 through day 10 or matching placebo. Forty-eight patients with chronic motor incomplete SCI finished the study, and 100-, 200-, and 400-mg oral doses of HP184 taken once daily were reported to be safe and well tolerated.

Acute SCI Trials

A number of strategies have been employed to promote the regeneration of cells within damaged spinal cords. These range from adding growth factors, to extracellular matrix inhibition, to the transplantation of various cell types. In the recent past, stem cells, Schwann cells, olfactory ensheathing cells, and macrophages have been separately transplanted into damaged spinal cords in animal models in an attempt to induce regeneration.34 These experiments have led to the development of some studies within humans.

There are three international regeneration trials that have been conducted recently or are in progress currently. In Beijing, China, Huang et al.35 are experimenting with transplanting olfactory ensheathing cells into the spinal cords of injured patients. The olfactory ensheathing cells are harvested from the glomerular layers of the olfactory bulb and then cultured in a tissue culturing system for 2–3 wks before being transplanted. A total of 171 patients have undergone olfactory ensheathing cells transplantation and have had their function assessed by the ASIA classification system before surgery and at 2 and 8 wks after surgery.35 “Most” patients are said to regain 2 levels of function and 3–5 levels of sensation within weeks of surgery. Overall, the authors report an improvement in spinal cord neurologic function, although there was no control group included for comparison with the experimental treatment, and the authors recommend further research to investigate the long-term outcome of the intervention.35

A study conducted in Russia by Rabinovich et al.36 investigated the subarachnoidal implant of fetal nervous and hematopoietic tissue cells into 15 patients presenting with severe cervical or thoracic-level SCI. There were between one and four separate surgeries conducted for each patient, and the outcome was measured by Frankel classification. Six patients reported an improvement from Frankel class A to C, five patients reported improvement to class B, and four patients had no improvement. No serious complications due to cell transplantation were noted.36

Tim Geraghty, Alan MacKay-Sim, and colleagues in Brisbane, Australia, are conducting a phase I trial in collaboration with Griffith University called the Regeneration of Human Spinal Cord Injuries with Olfactory Ensheathing Glia (OEG). Olfactory ensheathing glia cells from the nasal mucosa of chronic SCI patients were isolated and cultured, and 15 million olfactory ensheathing glia cells were then transplanted back into the spinal cord of each patient.

Furthermore, there are several SCI trials on regeneration currently in progress or that have recently been conducted in the United States. To begin, the Autologous Incubated Macrophages for Patients with Complete Spinal Cord Injuries study is currently recruiting patients for a phase II study.24,26 This multicenter, randomized, open-label trial has been designed to assess whether incubated macrophages would support axon regrowth at an SCI site, thus promoting the recovery of nerve function.24 The trial will measure both the safety and the efficacy of macrophage transplantation for 60 patients. The surgical intervention is conducted within 14 days of the SCI. A similarly designed trial is being conducted in Israel to assess the efficacy of transplanted macrophages for ASIA A–classified SCI patients.26 However, this study does have a parallel design, with two thirds of the patients receiving the experimental intervention and one third of the patients as control.

Another method for neuronal regeneration is by drug interventions that promote neural protection and growth. Studies using the experimental drug BA-210 are currently recruiting for phase I and phase II clinical studies to assess the safety and
The pharmacokinetics of the drug, and the neurologic status of the patients after treatment, will be assessed. The trial is designed to be a nonrandomized, open-label, uncontrolled, crossover study.

**CURRENT OUTCOME MEASURES IN SCI RESEARCH**

**Ralph J. Marino, MD, MSCE**

**Identifying an Appropriate Outcome Measure**

The success of a clinical trial depends in part on the appropriateness of the outcome measurement used to assess the change in a patient’s state before and after treatment. In the rehabilitation field, choosing an appropriate outcome tool can be a significant challenge for several reasons. Typically, more than one outcome is relevant to the intervention being assessed, and relevant outcomes are often affected by variables outside of treatment. Also, even good measurement tools rarely reflect the specific interest of the patient, although ultimately, improving a patient’s quality of life should be the top priority of a treatment.58

In the revised *International Classification of Functioning, Disability, and Health*,59 the World Health Organization defines the domains of clinical outcomes to include pathology, impairment, activity, and participation. This basic framework is useful for studies in SCI, which often utilize measurements of impairment, activity, and participation to determine an intervention’s success for a patient with SCI. Because improvements in activity and participation can occur via adaptive rehabilitation interventions, it is useful to assess the domain of functional limitations, particularly for interventions targeting pathology or impairment. Functional limitations fall between the impairment and disability (activity) domains in the Institute of Medicine model of disablement60,61 and are not affected by adaptive interventions.

It has often been a challenge to demonstrate the efficacy of SCI treatments. In part, this is because when an intervention and an outcome are considering the same domain, the relationship is direct and a greater effect is typically observed. For example, when treatment targets pathology, and the outcome considered is the change in the pathology, there tends to be a more significant, observable effect. SCI interventions are often directed at the level of pathology or impairment, whereas the outcome measured considers a more remote domain, such as activity. The indirect relationship tends to make the results of the intervention—the efficacy—seem less or insignificant.

The settings of clinical trials can create outcome measurement difficulties, as the testing environment often changes over the course of the trial. Clinical trials that begin while the patient is in the hospital often include follow-up assessments occurring 6–12 mos later, when the patient has returned to his or her community. Furthermore, the extended time needed to carry out a rehabilitative intervention, combined with the time required for the intervention to take effect, often makes the outcome interpretation more complicated and more costly. This is in contrast to medical interventions, which are often brief, with rapid effects.58

The patient’s changing social context can have a negative influence on the outcome measurement, as well.58 The confounding effects of the patient’s changing context are minimized by apt research design. This includes minimizing bias by randomization of the experimental and control groups, blinding of the participants and staff, and the focus of the following discussion: choosing an appropriate outcome measure.58

Wade58 compiled a list of questions to facilitate selecting the best, most appropriate measure of outcome (Table 10). It is recommended to begin the selection process by clearly defining why the outcome is being measured and for whom that data are being collected (which may include funding agencies, peer reviewers, journal editors, etc.). Next, the expected effects of the intervention should be specifically identified. This will help select an assessment tool that targets the expected result, adequately covers the range of outcomes that are possible, and is sensitive enough to detect an intervention’s effect. Data interpretation should not be hampered by floor and ceiling effects due to a measurement device that lacks range. Practical considerations are also important, such as the feasibility of correct administration of the assessment tool by the involved staff, the logistics of the testing, and the acceptability of the instrument to the patients. Finally, the data obtained by the measurement need to be meaningful and interpretable to the target audience.

**Specific Measures of Outcome Impairment Domain**

**International Standards for Neurological Classification of Spinal Cord Injury**

The gold standard for SCI neurologic assessment is the ASIA/International Spinal Cord Society Standards, now in its sixth revision.2 Most recent SCI trials assess neurologic and motor impairment by the Standards, which utilize sensory scores originally established by the NASCIS. The Standards have similar motor function scores, as well, except that five muscles are considered per extremity, instead of the seven used in the NASCIS. In par-
ticular, the trials conducted in Sygen,62 the Acorda clinical trials of fampridine, the HP184 trials, and several other planned studies use the sensory and motor exam from the Standards as an impairment measurement device, either as an outcome measure or to define inclusion criteria.

The individual sensory and motor scores are summed and used as a measure of impairment, and they are also used to determine the level (sensory, motor, and neurologic) and the severity of injury, by applying definitions found in the Standards booklet or reference manual.3 Severity of injury is graded using the AIS, a modification of the Frankel scale.2 The intervention being assessed and a prediction of the likely outcome help to determine which portions of the Standards will best detect a change in impairment. Successful usage of the Standards requires consistent, accurate motor and sensory examination by research personnel. This requires specific training, as clinical practice methods often differ from and may be less rigorous than the procedures recommended in the Standards. Furthermore, establishing a classification of impairment requires training to produce reliable scores.

Overall, the motor and sensory scores provide reliable measures of SCI impairment. Interrater reliability studies have indicated similar results for pin-prick scores (0.96), light-touch scores (0.96), and motor scores (0.98), although a closer analysis of subgroups within those areas does reveal more rater variability in scores.63 However, with successive versions of the Standards, more detailed, concrete definitions of the classification elements have promoted an increase in the reliability of sensory and motor-level designations (Table 11). This in turn, has resulted in a greater reliability, overall, for the determination of the AIS classification (Table 11). As mentioned previously, accurate and reliable classification occurs only with training, as demonstrated by the low levels of agreement in the third group in Table 11 (1992 Standards), who had been trained in how to examine but not how to classify SCI.

As was found for methylprednisolone,16 it is likely that some of the interventions under development for acute SCI will have a narrow therapeutic window. For an early-phase invasive clinical trial, it is desirable to limit enrollment to patients with a complete injury. However, the ability to accurately determine completeness of neurologic injury shortly after injury has been questioned. Because patients with SCI can spontaneously convert to incomplete and recover motor function, Burns et al.14 conducted a study to consider the reliability of the early designation of “complete” by the Standards. The study found that the neurologic status of 6.2% of patients (5 of 81) classified as AIS A within 2 days of their injury converted to AIS B in the follow-up assessments a week later. However, when patients with other confounding factors that affected the reliability of the exam (Table 12) were excluded from the cohort, only 2.6% of AIS A–classified patients converted to an AIS B classification after a week (1 of 38), and none had regained motor function at the 1-yr assessment. The study concluded that proper inclusion criteria could eliminate patients who may not reliably be designated as complete by the Standards, creating a population appropriate for an early intervention trial in SCI.

Changes in AIS grades from injury to various

<table>
<thead>
<tr>
<th>TABLE 10</th>
<th>Questions that will assist the selection of an outcome tool for a spinal cord injury study58</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Question</strong></td>
<td><strong>Psychometric Term or Question</strong></td>
</tr>
<tr>
<td>Will the data collected using this measure answer the clinical question?</td>
<td>Is it valid for this purpose?</td>
</tr>
<tr>
<td>Does the measure cover the whole range of possible activities or impairments without including items that are not relevant?</td>
<td>Content validity and avoidance of floor or ceiling effects</td>
</tr>
<tr>
<td>Do I know how much variability there will be in the data, and is that satisfactory?</td>
<td>What is its reliability when used as I will use it?</td>
</tr>
<tr>
<td>Is the measure going to deliver data that are able to discriminate or detect the change or difference that I am interested in or expect to find?</td>
<td>What is its sensitivity, and is that adequate?</td>
</tr>
<tr>
<td>Will the measure be correctly used by staff and accepted by the patients so that I get a full dataset under the circumstances? Is it sufficiently short and simple?</td>
<td>Is the measure feasible?</td>
</tr>
<tr>
<td>Will anyone reading the results of my study understand the data given by this measure?</td>
<td>How communicable is the result given by this measure?</td>
</tr>
</tbody>
</table>
Follow-up points have been reported, and they are somewhat useful in predicting recovery after traumatic SCI. However, prognosis is mixed for those with initial AIS grades of B and C. The data shown in Table 13 describe the percentage of patients who had AIS grade changes from initial evaluation to the time of discharge from rehabilitation in a study of traumatic SCI patients. Furthermore, the study reported that although only 13.3% (5.2%) of AIS A patients converted to motor incomplete by discharge ($P < 0.01$), a full 53.6% (54.6%) of AIS B patients had a conversion ($P < 0.001$). This variability of outcome in patients with incomplete SCI makes it difficult to perform studies on such patients during the acute period.

There are limitations to using the ASIA motor scores to assess outcomes. Change scores can be misleading when comparing different AIS grades. The maximum motor score of 100 points results in a ceiling effect on patients with an initial AIS grade of D. The observed improvement in motor scores is limited by the scoring process. For example, the improvement in patients with AIS grade D is numerically smaller than improvement in patients with AIS grade C, although grade D patients start and end with higher motor scores than grade C patients. In other words, different grade levels have different baseline starting points and therefore unequal amounts of possible improvement. This makes changes within one grade level difficult to compare in magnitude with a numerically similar change within a different grade level.

It is important to realize that the ASIA motor score is derived by summing individual muscle scores that are measured on an ordinal scale. The ASIA motor score therefore is not an interval measure. Recent metric analyses of the ASIA motor score have indicated that separating the upper and lower extremity scores retains useful information that can be lost in the composite motor score.

Evaluating the extremity scores separately enables a broader range of coverage of abilities, likely because the two-extremity limb scores function as separate scales (Fig. 3). Consequently, presenting the motor extremity scores independently promotes a better prediction of function, probably allowing a better interpretation of outcome.

When the ASIA classification system was originally developed, the ASIA D motor classification was limited to patients who had the capacity to walk. Eventually, the definition was modified to reflect the percentage of key muscles below the injury level with antigravity strength ($\geq 50\%$) or better, irrespective of the ability to walk. A further adaptation for a Sygen study of the ASIA D classification (A–C classifications remained unchanged) generated the Modified Benzel Scale. This scale expanded the ASIA D classification by closely defining a patient’s ambulation. The distance traveled, difficulty endured, and required assistance are considered when assigning a class in the Modified Benzel Scale. The Modified Benzel Scale is not widely used, and other measures of ambulation are being evaluated (see below).

Although manual testing of key muscles to derive a motor score is reliable, manual muscle testing of individual muscles is less so and may be too insensitive to detect clinically important changes in a muscle. Myometry measurements can better detect changes in strength for individual muscles and indicate continued improvement in strength when manual muscle test scores have plateaued.

### Measures of Functional Limitation

To determine if a change in impairment makes a practical difference to a patient, the functional limitation is measured. Functional limitations are the sum effect of patients’ impairments on their ability to interact with their environment. Measures of functional limitation consider actions, such as reaching, not actual activities or tasks that a person engages in, such as lifting a book off of a

---

**TABLE 11** Reliability in classification of American Spinal Injury Association Impairment Scale (AIS) measurements

<table>
<thead>
<tr>
<th>Year of Standards</th>
<th>Agreement,</th>
<th>Sensory Level</th>
<th>Motor Level</th>
<th>AIS Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>1987</td>
<td>64</td>
<td>66</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>1989</td>
<td>65</td>
<td>85</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>1992</td>
<td>63</td>
<td>32–45</td>
<td>54–72</td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>66</td>
<td>94</td>
<td>93</td>
<td></td>
</tr>
</tbody>
</table>

* a Untrained.

**TABLE 12** Factors that may affect examination reliability

<table>
<thead>
<tr>
<th>Mechanical ventilation</th>
<th>Intoxication</th>
<th>Sedation</th>
<th>Closed head injury</th>
<th>Psychiatric illness</th>
<th>Language barrier</th>
<th>Severe pain</th>
<th>Cerebral palsy</th>
</tr>
</thead>
</table>
shelf. For example, reaching may be limited not only by weakness but also by pain, spasticity, contracture, and other impairments. Functional limitations are properties of the individual (similar to impairments) rather than environmentally influenced (such as activities). Getting a book off a shelf may be improved by lowering the shelf, whereas reaching overhead will not be affected. The few assessment tools available to measure functional limitation will be discussed herein.

**Grasp and Release Test**

The Grasp and Release Test assesses the ability to move specific objects of different weights and sizes, and it requires static lateral or palmar prehension with minimal arm and trunk motion. The test uses six simple, standardized objects to measure functional limitations of the hand.70 The number of times each object can be moved from one spot to another in 30 secs is recorded. Although the Grasp and Release Test was instrumental in evaluating the effect of the Freehand System, an implantable upper extremity neuroprosthesis, it is limited to evaluating the two grasping patterns provided by the neuroprosthesis.

**Capabilities of Upper Extremities Instrument**

In 1998, the Capabilities of Upper Extremities (CUE) instrument was developed to rate the difficulty of performing certain actions on a 1–7 scale.71 The Capabilities of Upper Extremities instrument is a 32-question tool, with 15 items for each extremity and two bilaterally directed questions. Analyses have suggested good test–retest reliability (intraclass correlation coefficient of 0.94), validity, and homogeneity;71 however, further data are currently being collected to assess the sensitivity of the Capabilities of Upper Extremities instrument in changes in function. The Capabilities of Upper Extremities instrument has been used successfully to evaluate functional improvement after upper extremity reconstructive procedures and after Freehand System® implants.72

<table>
<thead>
<tr>
<th>AIS Grade at Admission</th>
<th>AIS Grade at Discharge, % (1 yr After Discharge)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
</tr>
<tr>
<td>A (n = 482)</td>
<td>84.6</td>
</tr>
<tr>
<td>B (n = 129)</td>
<td>7.8</td>
</tr>
<tr>
<td>C (n = 159)</td>
<td>3.1</td>
</tr>
<tr>
<td>D (n = 72)</td>
<td>0</td>
</tr>
</tbody>
</table>

**Measurements of Ambulation**

Ambulation is somewhat difficult to put into a domain of function. The domain is somewhat influenced by the definition used. It is a complex action and could be considered to fit in the functional limitation domain. It is more often viewed as an activity, in which braces, assistive devices, and other adaptive measures may influence function. As defined in the International Classification of Functioning, Disability, and Health, when measured in a standard environment, it is *capacity* of ambulation that is being assessed; when in the usual environment, it is *performance*.

The ability of a patient with SCI to ambulate can be described by gait variables and symmetry, the requirement of assistive devices or braces, and measurements of distance with respect to time.73 Field-Fote et al.73 have defined criteria for five levels of ambulation (Table 14); however, the definition of “better” ambulation remains elusive. Should a change in ambulation be defined by the criteria of less assistance, less equipment, or less energy required? Should ambulation be considered improved if there is less assistance at the cost of a slower speed, or if there is less energy used but only by employing leg braces? It is clear that the best way to assess ambulation will come secondary to the development of a more clear definition of what improvement entails.

**Walking Index for Spinal Cord Injury**

The Walking Index for Spinal Cord Injury (WISCI) is a recently developed tool that is gaining acceptance as a measure of ambulation.74 The WISCI was patterned after a scale used in animal research to describe the quality of a rat’s gait. The WISCI (and the revised version, WISCI II75) scale rate ambulation ability based on the amount of devices, braces, and personal assistance a patient requires to walk 10 m.74,75 The original analysis of the WISCI scale indicated a high reliability, demonstrated by 100% interrater agreement in the scoring of 40 video clips.76 Furthermore, the validity of the scale was shown by a retrospective anal-
ysis of 103 patients recovering from SCI. The initial ASIA grades correlated to the final WISCI levels \((P < 0.001)\), and there was monotonic improvement in 94% of the subjects.\(^7\) A comparison of the WISCI scale with other measures, such as the walking portions of the Barthel Index, FIM\(^7\), and Spinal Cord Independence Measure, indicated a high sensitivity to walking recovery, as demonstrated by the patient’s score distribution at discharge.\(^7\) The WISCI describes the method of ambulation on an ordinal scale of progressively fewer adaptations but does not assess speed or efficiency of gait. Therefore, it must be augmented with other measures in clinical trials.

**Tests of Walking**

Speed or energy expenditure of ambulation can be measured by the Timed Up-and-Go test (TUG, a walk of 25 feet and then the return), a 50-foot walk (alternatively, a 10-m walk), or a 6-min walk. The latter test is an endurance measure, whereas the former tests assess short-distance ambulation ability. Recently, these three tests were evaluated and compared in SCI.\(^7\) Intrarater and interrater reliability of all three tests was high, \(>0.97\).\(^7\) Reliability of the TUG and 10-m walk was less in poor ambulators, defined as WISCI levels 0 –10. Thus, any of these tests may be useful in evaluating ambulation in SCI, with the 6-min walk having an advantage, if poor ambulators are studied.

**Measurements of Activity: Performance**

**FIM**

The motor subscale of the FIM is a reliable means for differentiating gradations in activity within the SCI population. The motor subscale of the FIM is a 13-item, seven-level scale that is designed to assess the amount of help required for a person to perform basic activities of daily living.\(^7\) The FIM also includes a cognitive subscale that is not useful for discriminating levels of activity for SCI patients, as most will score well, unless the patient has a concomitant head injury. Analysis of the motor subscale of the FIM has indicated an internal consistency (Cronbach’s alpha) of 0.94 in traumatic SCI.\(^7\) The intraclass correlation coefficient for the motor subscale of the FIM was 0.96 in a large sample of patients undergoing inpatient rehabilitation.\(^7\) However, the FIM does have limitations as a measure of performance in clinical trials for neurologic recovery in SCI. These limitations include a burden-of-care focus, limited range of activities and difficulties, and assessment focused on performance rather than patient capacity. Because performance is influenced by environment, when the study extends from inpatient to outpatient settings, the reliability of the FIM may be compromised by varied discharge environments and by different methods of administration (generally by observation for inpatients and self-report for outpatients).

**Quadriplegia Index of Function**

The Quadriplegia Index of Function (QIF) was developed by Gresham et al.\(^8\) in 1980 to replace the less sensitive Barthel Index. It contains nine areas of activities of daily living and a tenth item that assesses personal care and health maintenance. Certain categories within the QIF, such as feeding, have been found to be more sensitive than FIM scores, as indicated by a higher correlation of the QIF feeding score with the ASIA upper limb motor score (Rho = 0.90 vs. 0.53, \(P < 0.01\)).\(^8\) Each item is given a score between 0 and 4, and overall, the test–retest reliability for the nine areas ranges from 0.55 to 0.95. However, the entire scale is not practical, or even necessarily applicable, depending on the assessment setting. Ceiling effects limit the use of the QIF for the assessment of activity in patients with paraplegia. A short form of the QIF, consisting of six items from five different categories, has been found to give results comparable with 37 items from seven different categories of the full-length QIF.\(^8\)

**Spinal Cord Independence Measure**

The newest addition to the physiatrist’s armamentarium for assessing activity level is the Spinal Cord Independence Measure. Originally developed by Catz et al.\(^8\) in 1997, the Spinal Cord Independence Measure has already been revised to create a measure with a higher sensitivity to change than the FIM.\(^8\) The revised Spinal Cord Independence Measure has good interrater reliability as well, with \(>80\%\) of scorings by two independent examiners.

![FIGURE 3 Graphic representation of the two limb scores.](image-url)
to be in total agreement for 13 of 18 listed functions.\textsuperscript{85} Lower levels of agreement were found for bed mobility and bowel management. Because of its newness, the Spinal Cord Independence Measure has not been thoroughly tested in clinical trials.

**Future Directions in SCI Measures of Outcome**

The International Spinal Research Trust commissioned a clinical initiative to improve clinical and physiologic assessments for determining the levels and severity of SCI and to reliably monitor recovery. Part of this research involved studying a number of quantitative sensory tests, including the light touch threshold test, the vibratory perception threshold, the thermal threshold, and the axon-reflex flare response.\textsuperscript{86}

Some noninvasive electrophysiologic techniques are available to assess neuronal activity of the spinal cord, including motor-evoked potentials via transcranial magnetic stimulation and reflex tests of the erector spinae muscles.\textsuperscript{86} The former test utilizes transcranial magnetic stimulation of the motor cortex to induce a motor-evoked potential at a measurable threshold and latency in the limb, erector spinae, intercostal, or internal oblique muscles. A comparison of SCI patients with control subjects indicated that complete thoracic SCI patients respond to a lower threshold transcranial magnetic stimulation above the lesion.\textsuperscript{86} As this is a characteristic response of SCI-injured patients to transcranial magnetic stimulation, the technique may be useful for monitoring the recovery process.\textsuperscript{86} Reflex testing of erector spinae muscles involves measuring short- and long-latency responses to tapping the muscle or spindles process. Patients with complete thoracic SCI lack the long latency response found in neurologically intact controls. These techniques may be extremely useful in monitoring motor recovery in the thoracic myotomes where manual muscle testing is not possible.

Functional magnetic resonance imaging has recently been applied to the study of spinal cord function.\textsuperscript{87} Ströman et al.\textsuperscript{87} applied thermal stimulation (10° Centigrade) to the L4 dermatome of each leg in volunteers with complete and incomplete SCI. Activity was seen consistently in the lumbar cord, although patterns of activity in the thoracic cord differed for complete and incomplete patients and for incomplete patients who could or could not perceive the cold stimulus.\textsuperscript{87} This demonstrates that functional magnetic resonance imaging can map neuronal function for the entire spinal cord without any need for sensory perception or voluntary motor activity below the injury level. This can help provide an accurate assessment of SCI injury.

Finally, for a comprehensive understanding of the effects of a therapy, the quality of life must be considered. This largely subjective concept is an assessment of patients’ perception of their pathology, impairments, activities, and participation within the context of their lives.\textsuperscript{58,88} There are >1200 general patient-centered outcome tools that are purported to measure quality of life.\textsuperscript{58} There is a trend toward the development of disease-specific measures; some examples of relevant tools for SCI patients are the Craig Handicap Assessment and Reporting Technique,\textsuperscript{89} the self-report FIM,\textsuperscript{90} the Satisfaction With Life Scale,\textsuperscript{91} and the Community Integration Questionnaire.\textsuperscript{92} Quality-of-life scales are hailed as patient centered because of their focus on the patients’ perspectives on their disease and treatment.\textsuperscript{58} They are not a substitute for measurements of treatment outcome, functional limitation, or participation; rather, they are an important adjunct to a comprehensive assessment of the effects of a therapy.\textsuperscript{93,94}

<table>
<thead>
<tr>
<th>Table 14 Criteria for levels of ambulation\textsuperscript{73}</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physiologic ambulation</strong></td>
</tr>
<tr>
<td>The endurance, strength, or level of assistance required for walking makes ambulation not practical or functional.</td>
</tr>
<tr>
<td><strong>Limited household ambulation</strong></td>
</tr>
<tr>
<td>The patient may be able to walk in the home but is limited by endurance, strength, or safety.</td>
</tr>
<tr>
<td><strong>Independent household ambulation</strong></td>
</tr>
<tr>
<td>The patient can walk continuously for distances that are considered reasonable within the home.</td>
</tr>
<tr>
<td><strong>Limited community ambulation</strong></td>
</tr>
<tr>
<td>The patient can walk outside the home and can manage doors, low curbs, and ramps. A wheelchair may be used for long distances.</td>
</tr>
<tr>
<td><strong>Independent community ambulation</strong></td>
</tr>
<tr>
<td>The patient walks for distances of approximately 400 m at a speed of ≥50% of normal and can manage all aspects of walking safely, including curbs, stairs, and doors.</td>
</tr>
</tbody>
</table>
tion must be considered. For a trial targeting pathology in the spinal cord, demonstrating improvement in electrophysiologic variables or even impairment is not sufficient. It is important to demonstrate that a meaningful improvement occurred by detecting changes in functional limitations or activities. When trials target the acute period after SCI, improvements in impairment and functional limitations will bolster the contention that improvements in activities were due to the intervention rather than adaptations employed during the rehabilitation process.

REFERENCES


November 2005 Spinal Cord Injury Clinical Trials S95
77. van Hedel HJ, Wirz M, Dietz V: Assessing walking ability in


Questions for CME Credit

Using the Answer Key on page S100, select the response that best answers the question or completes the sentence.

1. Which term best describes the most caudal segment of the spinal cord with normal sensory and motor function on both sides of the body following SCI?
   a. Zone of partial preservation.
   b. Incomplete SCI.
   c. Complete SCI.
   d. Partial innervation.
   e. Neurological level.

2. Which of the following are TRUE?
   a. The National Acute Spinal Cord Injury (NASCIS) clinical trial I failed to show a difference between experimental and control groups.
   b. The NASCIS II trial was the first large, multicenter controlled SCI trial.
   c. The Sygen Multicenter Acute Spinal Cord Injury Study (SMASCIS) was the first large, multicenter trial to conclusively demonstrate efficacy for an SCI treatment.
   d. Both A and C are correct.
   e. Both A and B are correct.

3. Model SCI systems (MSCIS) can be a resource for:
   a. The recruitment of patients for an SCI clinical trial.
   b. The provision of facilities for an SCI clinical trial.
   c. Training for trials development and conduct.
   d. The provision of a variety of personnel with diverse, specialized expertise in the various stages of clinical trials research and development.
   e. MSCIS can assist with all of the above.

4. The optimal design for a rehabilitative SCI clinical trial is:
   a. A randomized, controlled, double-blind design.
   b. A controlled, crossover, single-blind design.
   c. A randomized, controlled, parallel, single-blind design.
   d. An open label, single-blind design.
   e. A randomized, controlled, crossover design.

5. Which ASIA motor score level is limited by ceiling effects that should be taken into account when considering a patient's improvement?
   a. ASIA A
   b. ASIA B
   c. ASIA C
   d. ASIA D
   e. None of the above.

6. The precedent for clinical trial design for SCI was established by a trial that investigated the effects of the drug:
   a. methylprednisolone sodium succinate
   b. 4-aminopyridine
   c. BA-210
   d. HP184
   e. amitriptyline

7. Confounding variables that can affect the outcome measured of an SCI clinical trial are:
   a. The setting of the clinical trial
   b. The social context of the patient
   c. The time required for the trial
   d. Both B and C are correct.
   e. A, B, and C are correct.

8. The use of randomization for an SCI clinical trial can:
   a. Help to minimize the misinterpretation of a therapeutic effect, when there was no real difference between placebo and treatment groups.
   b. Provide a standard for comparison of the experimental group.
   c. Help to minimize interrater reliability.
   d. Help to minimize the bias of the measurement administrator.
   e. Help to minimize the number of patients designated as motor complete.

9. Which of the following can be used to measure functional limitation?
   a. The Quadriplegia Index of Function (QIF)
   b. The Functional Independence Measure (FIM)
   c. The Grasp and Release Test
   d. A, B, and C are correct.
   e. Both A and B are correct.

10. Which of the following is a reliable means for assessing SCI patient activity level, although the tool tends to be focused on patient performance rather than capacity?
    a. The Quadriplegia Index of Function (QIF)
    b. The Functional Independence Measure (FIM)
    c. The Walking Index for Spinal Cord Injury (WISCI)
    d. A, B, and C are correct.
    e. Both A and B are correct.

Please note that in order to obtain CME credit for this activity, you must complete and submit the Evaluation Form and Answer Key on the following page.
Spinal Cord Injury Clinical Trials for Functional Restoration
Improving Care through Clinical Research
Project ID: 2923-ES-14

The Postgraduate Institute for Medicine (PIM) respects and appreciates your opinions. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. You must complete this evaluation form to receive acknowledgement of participation for this activity.

Please answer the following questions by circling the appropriate rating:

5 = Outstanding  4 = Good  3 = Satisfactory  2 = Fair  1 = Poor

Extent to Which Program Activities Met the Identified Objectives

Upon completion of this activity, participants should be better able to:
1. Discuss the role of the physiatrist in participating in, recruiting patients for, and evaluating SCI clinical trial objectives and outcomes. 5 4 3 2 1
2. Explain issues in SCI research protocols design and evaluation. 5 4 3 2 1
3. Describe trends that may be expected to have an impact on the future of rehabilitation medicine in clinical practice. 5 4 3 2 1
4. Describe the key multicenter and other major clinical trials currently underway for chronic SCI interventions aimed at improving functional status. 5 4 3 2 1
5. Describe the primary outcomes measures being utilized for evaluating functional status. 5 4 3 2 1

Overall Effectiveness of the Activity

1. Was timely and will influence how I practice 5 4 3 2 1
2. Will assist me in improving patient care 5 4 3 2 1
3. Fulfilled my educational needs 5 4 3 2 1
4. Avoided commercial bias or influence 5 4 3 2 1

Impact of the Activity

1. The information presented: (check all that may apply)
   ☐ Reinforced my current practice/treatment habits
   ☐ Will improve my practice/patient outcomes
   ☐ Provided new ideas or information I expect to use
   ☐ Enhanced my current knowledge base
2. Will the information presented cause you to make any changes in your practice? ☐ Yes ☐ No
3. If yes, please describe any change(s) you plan to make in your practice as a result of this activity:

________________________________________________________________________
________________________________________________________________________

4. How committed are you to making these changes? 5 (Very committed)  4  3  2  1 (Not at all committed)

(continued next page...)
Spinal Cord Injury Clinical Trials for Functional Restoration
Improving Care through Clinical Research
Project ID: 2923-ES-14

Future Activities

1. Do you feel future activities on this subject matter are necessary and/or important to your practice? □ Yes □ No
2. Please list any other topics that would be of interest to you for future educational activities:

Follow-up
As part of our ongoing continuous quality-improvement effort, we conduct post-activity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey:
□ Yes, I would be interested in participating in a follow-up survey
□ No, I'm not interested in participating in a follow-up survey

Additional comments about this activity:

If you wish to receive acknowledgement of participation for this activity, please complete the post-test by selecting the best answer to each question, complete this evaluation verification of participation and mail or fax to: Postgraduate Institute for Medicine, PO Box 260620, Englewood, CO 80163-0620; Fax: 303-790-4876.

Post-test Answer Key

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
</table>

Request for Credit

Name ________________________________ Degree ________________________________
Organization ____________________________ Specialty ____________________________
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I certify my actual time spent to complete this educational activity to be:
□ I participated in the entire activity and claim 1.5 credits.
□ I participated in only part of the activity and claim _____ credits.

Signature ______________________________________ Date Completed _______________