Experimental treatments for spinal cord injury:

what you should know
if you are considering participation in a clinical trial.

A guide for people with spinal cord injury, their families, friends & caregivers.

Provided by

ICCP

International Campaign for Cures of spinal cord injury Paralysis

*Cover image: photo montage shows a research scientist superimposed
over a tri-coloured micrograph of spinal cord tissue.*

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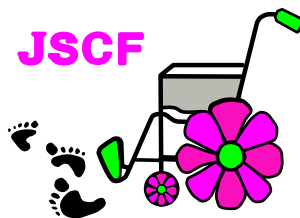Alain Privat[r]
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The ICCP is comprised of the following member organizations:

Christopher and Dana Reeve Foundation (USA) • Institut pour la Recherche sur la Moëlle épinière et l'Encéphale (France) • International Spinal Research Trust (UK) • Fondation internationale pour la recherche en paraplégie (Switzerland) • Japan Spinal Cord Foundation • Miami Project to Cure Paralysis (USA) • Neil Sachse Foundation (Australia) • Paralyzed Veterans of America (USA) • Rick Hansen Foundation (Canada) • Spinal Cure Australia (Australia) • Wings for Life (Austria)

Contents

Note: This guide is based on published scientific papers and the professional opinion of the authors as of 2006. The information will be periodically reviewed. The recommendations are subject to change as new knowledge becomes available. The contents of this document are intended to be an additional resource for you, and are not intended to substitute or replace current clinical treatments. Users of this guide should periodically review the material to ensure that the advice herein is consistent with: 1. the current reasonable clinical care they are receiving, and 2. the protocols of any experimental treatment being offered to improve their functional outcomes after spinal cord injury.

i Summary
Experimental treatment for spinal cord injury: what you should know if you are considering participation in a clinical trial.

After a spinal cord injury, patients are often told that there are no treatments available that will repair the damage. This is still true, and the advice is given to persuade people to focus on their rehabilitation rather than hoping for a miracle cure. However, great advances have been made in the science of spinal cord repair, and treatments that will improve the function of people with spinal injury are now emerging, although a complete cure is still not feasible (a list of potential approaches currently being examined is provided in the full booklet).

As these new treatments move from the laboratory to the clinic, they will need to undergo **clinical trials**. This booklet offers advice to you should you consider participating in a trial.

Why are clinical trials necessary?

It can be surprisingly difficult to find out if a treatment is safe and if it really works. Patients often believe they have got better as a result of a new treatment, but the improvement may not really have been caused by the treatment. There are two main problems.

Spontaneous recovery. Immediately after a spinal injury patients are often completely paralyzed. Most people will recover to some extent without treatment, and for a few fortunate people the recovery can be dramatic, almost back to normal. The rate of recovery is greatest in the first three months, but recovery continues for a year or even more. It is very difficult to work out whether recovery in an individual is due to this spontaneous recovery, or due to the effects of a treatment, particularly if the treatment is given soon after the injury. [see section 2]

The placebo effect. People with spinal injury are desperate to get better. After being given a treatment their belief and hope usually leads them to report an apparent improvement. In clinical trials, patients receiving a sham or placebo treatment usually report a considerable improvement in their condition, and this may be just as large an improvement as is reported by the patients receiving the experimental (sometimes called *active*) treatment. [see section 5, 6]

There is a real danger that treatments that do not really work or might even do harm might become standard medical care because they were not subjected to a proper clinical trial. [see section 6]

Why should you think carefully before enlisting in a clinical trial?

People with spinal injuries are understandably desperate to get better. Scientists have been working extremely hard to develop new treatments, and want very much to see their treatments help people with spinal injuries as soon as possible. The urge for both groups to cut corners is considerable. The majority of clinical trials will be well planned and carefully conducted. However there may be a few that should be avoided. This brochure, and the larger accompanying ICCP document should help you identify good clinical trials. [see section 5]

 A good clinical trial will be testing a treatment that has undergone extensive investigation in animals and will have shown a strong and repeatable effect. The clinical trial will be carefully designed to compare a group of patients receiving the experimental treatment with others receiving no treatment or a placebo.

Experimental treatments offered without having completed a trial. Some possible treatments may be offered to patients, usually by doctors who believe strongly that they will work. In the absence of a clinical trial in which the effects of the treatment are compared with a control group of patients receiving a placebo treatment, it is almost impossible to determine whether the treatment is really effective.

Treatments offered for material gain. Unfortunately, where patients are desperate for a cure, there is the opportunity for less scrupulous organizations to offer unproven treatments to those who can pay. You should not have to pay for any procedure specifically related to a clinical trial program, but you, or your health care insurance system, may have to pay for the current standard of medical care.

Creating new treatments for those with spinal injury is probably the most difficult thing that medicine has ever attempted. There is a very small chance that a treatment offered prematurely without completing a properly designed clinical trial will work, but it is more likely that it will be ineffective or even do harm. We advise very strongly that you should only participate in properly designed and conducted clinical trials of treatments for which there is compelling evidence of efficacy from animal experiments.
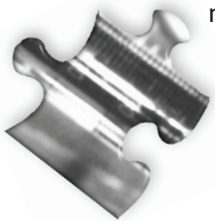
How are clinical trials structured?

 It takes three clinical trial steps, or *phases*, to qualify a treatment for human patients. [see section 4]

Phase 1 is to find out if the treatment is safe. A fairly small number of patients, usually between 20 and 80, are given the treatment, usually initially at a low dose, to see if there are side effects.

Phase 2 is designed to look for positive treatment effects, comparing patients receiving the treatments with a control group.

If a useful effect is seen in Phase 2, the trial proceeds to *Phase 3*. Here a larger number of patients, usually in several clinics, are given the active treatment or a control treatment. If the treatment shows a clear useful effect and no serious side-effects, usually in two separate Phase 3 trials, then it will be approved by the national regulatory agencies for clinical use.

Design of clinical trials: The key feature of most clinical trials is the comparison of a group of patients receiving the active (experimental) treatment with a control group, that either does not receive the treatment or receives an inactive placebo treatment. The only type of trial in which this is not the case is on e in which patients whose condition is very stable (this would mean patients 1 year or more after spinal injury) who act as their own control group, and are given a treatment to see whether their condition improves compared with their previous abilities. When the effect of a treatment on the experimental group is being compared with the outcomes from a control group, steps should be taken to make sure that the people doing the assessments are unaware of whether patients have received active or dummy treatments (this is known as blinding). In many trials the patients are also blinded to the group they have been assigned, although this type of blinding is sometimes hard to achieve with spinal injury treatments requiring surgery. [see section 4]

How would participation in a clinical trial affect you? Before anyone can be enrolled in a trial they must give informed consent. If a treatment has to be given very soon after spinal injury, some patients may not be fully conscious, and then their family can give consent on their behalf. Not all patients will qualify for a trial, because most trials will select particular groups of patients with particular types of injury. All trials have criteria because if the patients are too different from one another it may be impossible to find out if a treatment has worked. After enrollment, patients are randomly assigned to the active treatment or control group. After or during the treatment, there will be frequent follow up examinations, for which it will be necessary to attend the clinic. These examinations may include a full physical exam, blood tests, and tests of the ability to perform daily living tasks to assess spinal cord function. You should not have to pay for these visits.

What if you get assigned to the control group?

Most patients would obviously prefer to receive the active treatment. However, as we described above, it is impossible to decide if a treatment really works unless there are control patients with whom to make comparisons. If by mischance the treatment has an undesirable side effect, then being in the control group is an advantage. Patients participating in a trial should all benefit by receiving the current best care. The trial investigators will have a policy on what to offer members of the control group at the end of the trial. Rapid enrollment in a second trial is sometimes a possibility, as is receiving some form of approved treatment. If this is not clear, you may need to enquire. [see section 4]

What should you expect after a clinical trial?

At the end of the trial you are unlikely to be completely cured. Could you then obtain another treatment in a different trial? The enrollment criteria for some trials may exclude patients that have already received some types of experimental treatment. Those running the trial will have a policy on what to offer patients at the end. There is more information on this issue in the full document, and you can discuss it with the investigators running the clinical trial. [see section 8]

You have been invited to participate in a clinical trial. How can you decide?

Before entering any trial you or your relatives will have to give informed consent. [see section 5] Here are some of the things about which you should satisfy yourself.

Experimental evidence that the treatment works. Any treatment reaching clinical trials should have been tested in animals with spinal injuries, and should have produced a clear improvement without toxic side effects. It is important that this positive result has been published and reviewed by other scientists, and has been repeated several times, in different types of experimental spinal cord injury, and in more than one laboratory. If you ask you should receive a detailed account of this work. [see section 4]

Evidence that the treatment is safe. Before being applied to human patients any treatment should have gone through a series of safety tests. It may have already been tested in Phase 1 or 2.

Design of the trial. You should know whether you are being enrolled in Phase 1, 2 or 3. The trial should be registered with an appropriate government regulatory body. In a well conducted Phase 2 or 3 trial there will be a treatment and control group, and patients will be randomly assigned to one or the other. Steps should be taken to blind the assessors as to whether you are in the treatment or control group. There will be a number of follow-up examinations over a period, often as long as a year after the treatment, conducted in the appropriate clinic. You should not have to pay for these. At the end of the trial there should be a clear policy on what can be offered to patients in both the active treatment and control groups.

Where can you get advice?

You have a number of options:

- There are good websites run by the various spinal injury organizations that are members of the ICCP (see page 39). You can contact the foundations directly and ask for advice. Many of them are staffed by people who themselves have spinal cord injuries. Some government research agencies also have useful information on their websites (for instance the National Institutes for Health in the USA).

- Spinal injury researchers are generally pleased to offer advice if you ask them; it is best to do this by email. You can get names of researchers from the foundations.

- Most patients will have a regular physician, who will be prepared to offer advice or direct you to the most appropriate person.

- **Keep reading:** the rest of this document contains many more details about the information touched on in this summary. We start with an overview of the ASIA scale and spontaneous recovery, and then look at the risks of unapproved treatments. We examine in-depth the anatomy of a clinical trial, from Phase 1 to Phase 4, as well as the basics of trial design and pre-clinical studies. We discuss the ethics of clinical trials, bias, controls, and the importance of informed consent. We review some scales that are used to measure functional benefits, and outline some concerns that might arise regarding the possibility of taking part in a future trial after already participating in a trial. We introduce you to some experimental approaches to SCI currently being studied. Finally, we provide you with a list of questions that you can pose to a researcher inviting you to participate in a human study. This checklist might assist you in your decision whether or not to participate in the trial.

1 Why have we written this booklet?

This booklet is primarily directed to people living with a spinal cord injury (SCI), their families and friends. It may also be of value to health care professionals and scientists when discussing experimental treatments for SCI.

We aim to answer some of your concerns about experimental treatments and SCI clinical trial* procedures, but most importantly, we wish to provide you with a set of questions that should be answered to your satisfaction before you agree to accept an experimental treatment or participate in a clinical trial program (see section 10).

This document is based on published, peer-reviewed literature in reputable scientific and medical journals, as well as the opinions of a panel of experts drawn from across the globe. This panel consisted of professors and doctors with extensive scientific and clinical experience in SCI, many of whom have conducted SCI clinical trials, as well as people who are familiar with ethics and clinical regulatory practices. This SCI Clinical Guidelines Panel drafted an initial set of guidelines for the valid conduct of a clinical trial for SCI. These guidelines have been peer-reviewed and published in the journal, *Spinal Cord*.[1][2][3][4]

Around the world, the annual incidence of SCI (paraplegia and tetraplegia) varies by region from less than 20 per million people to more than 50 per million people.[5] However, with continuing improvement in medical care, as well as an increasing lifespan for people living with SCI, the worldwide number of survivors is now over two million people.

Scientists and doctors around the world are searching for innovative ways to treat SCI and improve functional outcomes, as well as quality of life after SCI. The list of experimental interventions, therapies, and assistive devices that have been developed in pre-clinical animal models is extensive. More importantly, if these potential therapies are to be accepted as valid treatments for people with SCI, then they will need to undergo clinical trials in the near future. Some early stage SCI clinical trials have recently been started and several more are at a late stage of pre-clinical animal testing.

> *"Each day we deal with patients and families desperately searching for answers to spinal cord injury. Until now, we have had woefully little to share with them to help answer their questions about clinical trials, human studies, and promising or questionable therapies. This booklet will provide an invaluable roadmap for all."*
>
> - Susan Howley
> Executive Vice President and Director for Research
> Christopher Reeve Foundation

However, one troubling fact is that some experimental therapies, such as cellular transplants into the injured spinal cord, have been introduced into clinical practice without a valid clinical trial program being completed. One of the aims of this document is to explain the differences between such practices and sound clinical trials using valid study designs.

The International Campaign for Cures of spinal cord injury Paralysis (ICCP) is an affiliation of 'not for profit' organizations, which aims to facilitate the translation of valid treatments for SCI from experimental studies in animal models through clinical trials to establish best clinical practices. You will find a list of member institutions on page 4 of this booklet.

The ICCP SCI Clinical Guidelines Panel elected to direct the initial set of guidelines towards the design of clinical trials for the increasing number of experimental cell-based and pharmaceutical drug treatments to protect or repair the injured spinal cord, whether at the acute or chronic stage of SCI. The reasons for this focus are the substantial risks and potential benefits for these types of treatments, and the fact that some of these treatments have either been offered without completing a clinical trial or will soon enter clinical trials. The members of the panel, whose names appear in the list of authors, volunteered their time and effort towards this project for two years (2004-06). The panel's travel and accommodation expenses were supported by the ICCP, with Vancouver-based ICORD providing all logistical coordination.

This booklet contains a discussion of the many factors that must be considered when designing clinical trials in SCI, and whether an individual should agree to participate in a trial or accept a treatment that has not been validated through a regulated clinical trial program. By adhering to logical clinical trial guidelines, we believe a legitimate path can be established for the validation of effective therapies that can improve both function and quality of life for people living with SCI.

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* terms defined in the glossary are underlined in red the first time they appear in the text

2 What are the chances that you will see some functional improvement after SCI *without* a drug treatment or transplantation of cells?

The degree of functional recovery expected to occur naturally or spontaneously after SCI depends primarily on the severity or extent of the spinal injury. The most common clinical evaluation tool used by doctors to classify the extent of SCI is the ASIA impairment scale (Fig. 1), initially developed by the American Spinal Injury Association (ASIA). Components of the ASIA scale have also been used to assess the results or "outcomes" of the few clinical trials completed to date.

The ASIA scale was developed as a method for classifying the neurological level and severity of a spinal injury[6] and is based on a careful assessment which maps any preserved sensory and muscle or "motor" functions

(Fig. 2). It is continually reviewed and refined by an international panel. One strength of the ASIA scale is that it requires little or no equipment to be completed.

ASIA IMPAIRMENT SCALE
- ☐ **A=Complete:** no motor or sensory function is preserved in the sacral segments S4-S5
- ☐ **B=Incomplete:** sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-S5
- ☐ **C=Incomplete:** motor function is preserved below the neurological level, and more than half of key muscles below the neurological level have a muscle grade less than 3
- ☐ **D=Incomplete:** motor function is preserved below the neurological level, and at least half of key muscles below the neurological level have a muscel grade of 3 or more
- ☐ **E=Normal:** motor and sensory function are normal

CLINICAL SYNDROMES
- ☐ Central Cord
- ☐ Brown-Sequard
- ☐ Anterior Cord
- ☐ Conus Medullaris
- ☐ Cauda Equena

Figure 1. The most common classification of SCI (ASIA Grades A – E)

Figure 2. The key muscle groups and sensations examined along the spinal cord. Each representative muscle is graded on the strength of contraction from 0–5, whereas perception of light touch or pin prick sensation is graded on a more limited scale of 0–2. Note: there is no reliable testing of motor function for the upper cervical spinal cord (in the neck) or for the thoracic spinal cord (in the chest).
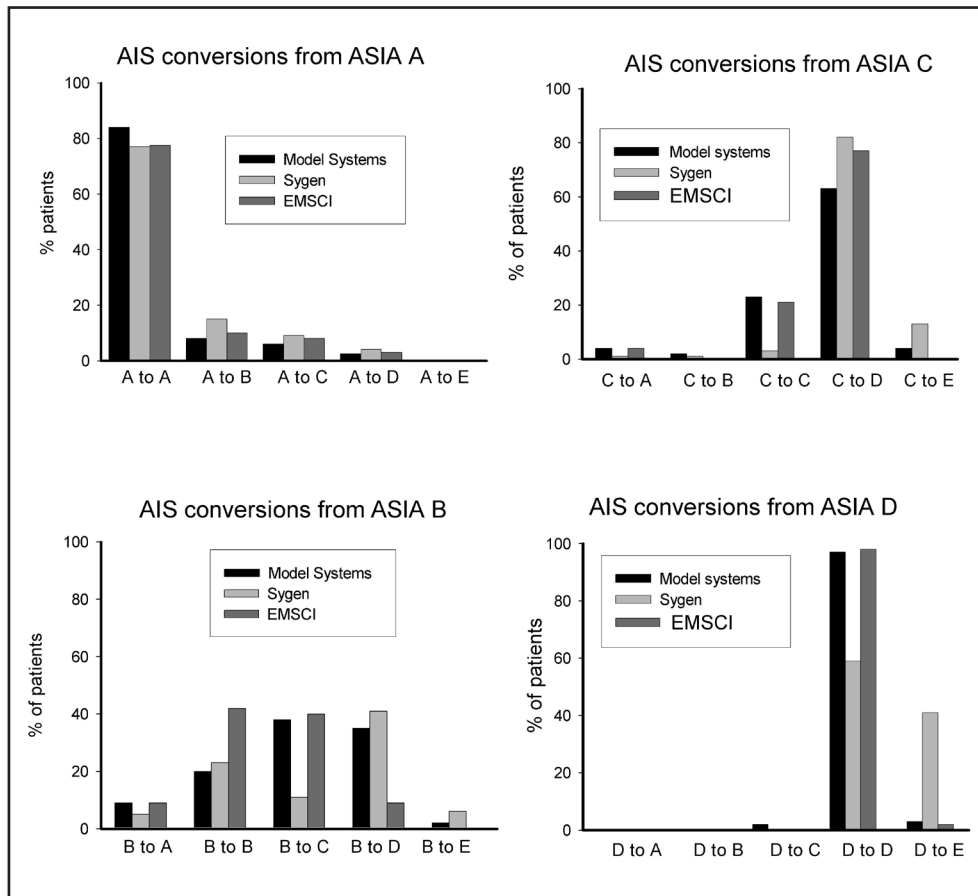
Figure 3. The percentage of people with a spinal injury converting from each initial AIS (or ASIA Impairment Scale) classification, sometimes called the ASIA grade. The initial classification is usually established within the first three days to four weeks after injury. In this figure, the classification of the ASIA grade has been re-assessed at the one year anniversary date after SCI and the percentage change from the initial classification is charted. For example, approximately 80% of individuals initially classified as ASIA A will remain as an ASIA A at the one year anniversary after SCI.

This information is drawn from the U.S. Model Systems database, the Sygen clinical trial database and the EMSCI (European Multicenter Spinal Cord Injury) databases. Even though there is more than twenty years between the time when some of the data was collected for the U.S. Model Systems versus the EMSCI databases, there is still some consistency in terms of the degree of spontaneous recovery after SCI that was observed in these two groups. With continually improving emergency services, acute care and rehabilitation, these data are likely to show an increase in recovery rates.

However, the scoring of the ASIA scale, and its subsidiary sensory and motor scores can still be relatively subjective. It requires rigorous training for a correct assessment to be made and for an accurate interpretation of the outcomes. Due to its relative simplicity and widespread adoption across the world, the ASIA scores have been used as an outcome tool to follow changes in neurological function after SCI, whether these occur spontaneously or as a result of a therapeutic intervention. Figures 1 and 2 show some of the functional differences between the different ASIA classification grades, which range from ASIA A through to ASIA E.

Individuals initially classified as having completeSCI, loss of sensory and motor function below the level of injury, are classified as ASIA A (Fig. 1 & 2) and have the most limited prognosis for regaining any additional function after SCI. Several studies suggest that approximately 80% of these individuals will remain as an ASIA A classification (Fig. 3). Individuals who initially have some sensory function as low as the anal sphincter but show no evidence of motor function below the level of SCI are classified as ASIA B. As many as 40% of those individuals initially classified as ASIA B may convert to an ASIA C classification, even though the majority of the recovered motor function may not be completely functional (Fig 3). On a more positive note, up to 40% of those initially classified as ASIA B may convert to an ASIA D classification where the majority of muscles do show functionally useful movement. Finally, the majority (60% to 80%) of those individuals who initially present as an ASIA C classification will recover to an ASIA D status (Fig 1 & 3). Many people with an ASIA D classification are able to walk independently.

Thus, even when the only signs of initial spared (preserved) function are for sensation (ASIA B classification), there is substantial evidence for functional improvement. On average, the functional outcomes improve dramatically for those individuals where there is initial evidence for the preservation of minimal motor function (ASIA C). Recent evidence indicates that those people with incomplete SCI (ASIA B-D) can continue to improve their functional abilities with vigorous and active physical rehabilitation after SCI.[7]

This leaves an individual with incomplete SCI the difficult decision of weighing the benefits versus the risks of an invasive experimental treatment, such as the direct transplantation of cells into the spinal cord or the infusion of a drug into their body. Will they regain more function or risk losing what they have already recovered? Difficult decisions like this require a dispassionate and objective assessment of all the risks and benefits, based on the available preclinical and clinical evidence.

3 What are the risks of undergoing a treatment that has not been approved by an appropriate regulatory agency?

There are potential risks for undergoing a treatment that has not been validated and approved by an appropriate national regulatory agency, such as the Food and Drug Administration (FDA) in the United States. The role of health regulatory agencies is to make sure that both the risks and the benefits of a particular treatment are quantified to certain minimum standards before they can be approved as safe and efficacious within the limits established by a valid clinical trial program. An individual who receives an unapproved treatment is unlikely to achieve a functional benefit that can be clearly attributed to that treatment, while risking unknown and potential harm.

General clinical trial guidelines have been accepted and ratified by most nations. They are in place to protect the public from the harm that could result from an unsubstantiated and unapproved treatment. For SCI, these could include:

1. increased and long-lasting pain,
2. further loss of function,
3. increased disability,
4. other medical dysfunction, and/or
5. death

Furthermore, should there be medical complications arising from an unapproved treatment, subsequent health care coverage and/or disability support payments may be lost. Depending on the treatment received, your participation in a future SCI clinical trial may also be limited or disallowed (see section 8).

Many people living with SCI, as well as their families, believe that health care providers in the developed world are slow to adopt new therapies that are sometimes made available in an emerging nation. In fact, SCI scientists, clinicians, and institutions (in developed nations) are very eager to provide any new treatment, but only when it has been validated in an objective and unbiased manner as safe and beneficial, using carefully developed standards.

4 What is a clinical trial, and what is the pre-clinical process for developing a therapeutic treatment for SCI?

A clinical trial is a research study in human subjects to determine the efficacy of a new therapy or drug. There are four phases (or levels) of clinical trials. All the phases of a clinical trial program are usually necessary for the appropriate regulatory body to grant the approval of the therapeutic for clinical use and each phase may involve a number of successive or parallel trials.

Phase 1- Safety Pilot : Phase 1 (or "pilot") trials begin with the first administration of the therapeutic intervention to a human subject (e.g. experimental drug, cellular transplant, rehabilitation strategy, or assistive device) and examines a number of aspects of the safety and interaction between the treatment and the subject, often in a small number of subjects. A Phase 1 study (see page 15) is usually based on extensive preclinical safety evaluations and designed with a built-in margin of safety

Phase I clinical trials test a new biomedical intervention in a small group of people (20-80) for the first time to evaluate safety (determine a safe dosage range, identify side effects, etc.).

Phase II clinical trials study the biomedical or behavioral intervention in a larger group of people (several hundred) to determine efficacy and to further evaluate its safety.

Phase III studies investigate the efficacy of the therapy in large groups of human subjects (from several hundred to several thousand), comparing the intervention to other standard or experimental interventions as well as to monitor adverse effects

Phase IV studies are conducted after the intervention has been marketed. These studies are designed to monitor effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread use.

between the highest doses and durations of treatment explored in animal studies and/or earlier human treatment protocols. Evaluation of safety is an important aspect of all phases of clinical development, but it is the primary outcome in Phase 1 trials, which can expose the most common adverse events (side effects or complications) of any intervention.

Another important aspect of Phase 1 drug studies is measurement of the pharmacokinetics, and potentially the pharmacodynamics of the therapeutic. Pharmacokinetics is the study of of what the body does to a drug, with emphasis on the time required for absorption, distribution within body tissues, the mode and extent of metabolism, or breakdown and the method of excretion. Pharmacodynamics is the study of what a drug does to the body, with emphasis on its biochemical and physiological effects of drugs, as well

as the mechanisms of drug action and the relationship between drug concentration and effect. In the case of cellular treatments, equivalent studies of the fate of implanted cells or tissues will be important to pursue, but may be much more difficult to implement.

Phase 1 trials may, but more often do not, include control subjects and are usually carried out in an "unblinded," or open label fashion, with both the participants and investigators knowing what drug is being tested and what dosages are being used. Phase 1 studies of non-invasive or minimally-invasive treatments (i.e. not requiring surgery) are often undertaken in healthy volunteer subjects. In contrast, many of the potential SCI therapies are likely to be invasive; thus most Phase 1 trials would be expected to only involve subjects with SCI. As a result, there is an opportunity to undertake a preliminary evaluation of the possible therapeutic benefit of the experimental treatment when it is first tested in humans. When this occurs the study is often re-labeled as a Phase 1/2a trial. Note that any efficacy (clinical benefit) data derived in a Phase 1/2a trial would not be a validation for that treatment, primarily because of the small sample size and the lack of blinded assessments.

Phase 2 - Therapeutic Exploratory: In Phase 2 trials, the primary objective shifts to the exploration of potential therapeutic effect when compared to an untreated or placebo control group. This is also the clinical phase where the most appropriate outcome measures to detect a potential therapeutic benefit are examined. Thus, a Phase 2 trial is designed to demonstrate the "activity" of an intervention: that is, to demonstrate that the intervention is associated with a positive change in relevant outcome variables, with less stringent statistical criteria than Phase 3 trials. There are a number of protocol designs for Phase 2 trials, but all trials at this stage should include control subjects and some form of blinded assessment where the person undertaking the outcome measurement and/or evaluating the outcome data does not know the treatment or control group to which the subject was assigned. The preferred Phase 2 design would be a Randomized Control Trial (RCT) where each participant is recruited prospectively (i.e. in a go-forward manner) and randomly assigned to either the experimental or control group of the study and where the investigators and if at all possible the participants, are blinded to which study group they have been assigned.

Another common characteristic of Phase 2 trials is the use of relatively restrictive inclusion criteria to ensure a more uniform study and thereby reduce random variations and outcomes. For example, it may not be optimal in a Phase 2 trial to simultaneously compare data from motor complete (ASIA A and B) with motor incomplete (ASIA C and D) subjects. To avoid comparing apples with oranges, many Phase 2 trials have different study groups of subjects (sometimes called trial "arms" or study "cohorts"), which are distinct from other groups and may be evaluated separately.

Even though most Phase 2 trials declare a primary clinical endpoint and outcome threshold, they should also evaluate a number of different clinical endpoints (secondary outcomes) to guide the selection of the most definitive primary outcome to be used later in a Phase 3 trial. It is not uncommon to undertake more than one Phase 2 trial to explore other target populations that might receive benefit from the therapeutic agent.

Phase 3 – Therapeutic Efficacy: Phase 3 clinical trials are generally the definitive or "pivotal" clinical trial phase and are typically undertaken as a randomized control trial. The objective is to confirm the preliminary evidence obtained at the Phase 2 stage with a statistically significant clinical benefit of the experimental treatment in a large group of subjects, usually across multiple study centers. These trials also provide the most informative safety data because they usually address at least a few hundred subjects and provide information on people who are treated, as well as people who are part of the placebo control group. A fair comparison can be made of the rate of occurrence of adverse events of all types, and a wide range of other clinical measures which are monitored in great detail, looking for the possibility of unexpected and undesirable changes.

Given that the Phase 2 trial may have been conducted on a well-defined subset of patients with SCI, it is also possible to consider including a broader spectrum of subjects in a Phase 3 study. Nevertheless, it is generally advisable to keep the design of Phase 3 studies close to that of the preceding Phase 2 trials so that the outcome is more predictable. Likewise, it is only possible to accurately estimate how many subjects would be required for a statistically significant Phase 3 trial if there is pre-existing data from a similar study using similar subjects.

If the Phase 3 investigation concludes with the valid demonstration of a statistically significant clinical benefit from the therapeutic and an acceptable safety profile, an application is usually made to the appropriate regulatory body for approval to market the treatment. Some jurisdictions, for example the United States, prefer that a second confirmatory Phase 3 trial be completed prior to approval of the treatment being granted, but there are many factors that can influence this requirement, including the relative benefits of current treatments. The submission for regulatory approval entails an enormous amount of documentation, regarding every preclinical and clinical study performed and the medical documentation of every subject, so that the regulatory

agency can perform its own independent analysis of the complete set of data regarding the safety and efficacy of the new intervention.

Phase 4 - Therapeutic Use: Phase 4 begins with marketing approval, labeling and introduction of the therapeutic intervention for clinical use for a specific type of disorder. It includes ongoing surveillance related to therapeutic safety, including possible drug interactions and contraindications, continued optimization of dose and therapeutic delivery regimens, as well as studies to delineate additional information on the intervention's risks, benefits, and optimal use.

Clinical trial protocol configurations and study designs: There are numerous ways to design trials and each has its particular strengths and limitations. An important concern for all clinical trials is the potential for bias, however unintentional, to influence the interpretation of clinical outcomes. There are varying degrees of blinding to control and limit who knows what treatment, if any, the subject has received. The first clinical trial is often an open label wherein the identity of the treatment received is known to both the investigators and participants. This should normally be reserved for Phase 1 studies that address safety. Open Label protocols have been used in the study of both drug and surgical SCI interventions in Phase 1 trials.[8][9][10][11][12]

The next level is a single blind study where either the clinical investigator or the subject, but not both, are blinded. For SCI trials where a surgical intervention is part of the experimental protocol, it may be necessary for the surgeon to know what is being undertaken in that subject. While it is preferred that the patients in both experimental and control groups remain blinded to the treatment received, this is not always possible. It is important, however, that the examiners assessing the outcomes remain blinded to the treatment provided. This may require monitoring to assure a subject does not disclose to the assessor to which treatment group they have been assigned.

Ethical or legal difficulties may interfere with the use of blinding when it entails sham operative procedures. Nonetheless, sham surgical trials have been implemented in neurological disorders in recent years, and proven critical to understanding and interpreting the results,[13,14] so they should be considered in SCI trials as well. Once again, outcome assessments should be blinded using such techniques as identical bandaging of the overlying skin during assessments by independent examiners. Single blinding of a primary outcome

There are many ways to design a clinical trial. Trials can be designed as "open label," "single blind" or "double blind"

measurement has been utilized in recent Phase 2 randomized controlled trials using a patient's own white blood cells (known as autologous macrophages) in the treatment of SCI.[12]

Finally, a double blind design is optimal, where neither the participating trial subject nor the investigators, institutional staff or sponsoring company are aware of the treatment each subject has received during the trial. Ideal blinding would ensure that the treatments cannot be distinguished by subjective experience, appearance, timing, or delivery method by any of the subjects, investigators, research staff, or clinical staff. This should be maintained throughout the conduct of the entire trial from determination of eligibility through evaluation of all outcomes. Double blind design has been used in a number of pharmacological trials in SCI including investigations of methylprednisolone and GM-1 ganglioside in acute SCI,[15][16][17][18][19] 4-aminopyridine in chronic SCI[20][21] and in surgical trials for Parkinson's disease.[10]

Parallel Group Design is the most common clinical trial design for pivotal Phase 3 trials. Subjects are randomly assigned (often in equal numbers) to one or more treatment arms, each testing a different treatment or combination of treatments. The treatments might include the investigational product at one or more doses, and one or more control conditions such as an inactive placebo,[16][22] or a comparative drug.[15][23] A current treatment may have to be present in both active and control arms of the study, such as methylprednisolone in the multi-center GM-1 trial.[19] Assumptions underlying the parallel group design are less complex and more robust than those of other designs.

Crossover Designs randomly assign the order in which subjects are exposed to a sequence of two or more treatments (e.g. placebo control and experimental therapeutic). Hence, subjects receive the treatment and placebo at different times, and act as their own controls for treatment comparisons. This approach has been used in the evaluation of 4-aminopyridine in chronic injury.[20] When subjects act as their own controls, the functional capacity of the subject should be stable (unchanging) prior to application of the experimental treatment. Because the functional capacities of a person with acute or sub-acute SCI can vary dramatically over a short period of time, this type of design will normally be restricted to studies of chronic SCI, where the functional capacity to be assessed is expected to be relatively stable.

The relevant effects of treatment should develop fully within the treatment period and reverse following removal of treatment. One important concern of a

crossover design is the possibility of residual effects (carryover influence) of the experimental or placebo control treatment, which can influence the outcome after the subject has crossed over to the opposite treatment arm. The "washout" time period between treatment arms should be sufficiently long to allow the complete reversibility of any treatment effect. An advantage of the crossover design is that it may allow a reduction in the number of subjects or assessments needed to achieve a specific statistical power.

Pre-clinical process for developing a therapeutic treatment for SCI: Most people living with SCI want to understand how a scientific discovery becomes a valid therapy. Listed below are some of the fundamental steps in this process. Please note that there are no government regulations restricting the claims made by the authors of pre-clinical studies using animal models. Instead, scientists are constrained by the healthy and often demanding skepticism of the peer-review process that is used by any legitimate scientific or medical journal. For many reasons, scientists often do not complete all the elements of experiments that the majority of the scientific world would like to see accomplished before a therapeutic discovery is introduced for translation to human treatment. Fortunately in most developed countries, there are several safety barriers that must be passed, to the satisfaction of the appropriate regulatory agency, before an investigational treatment is given to human subjects.
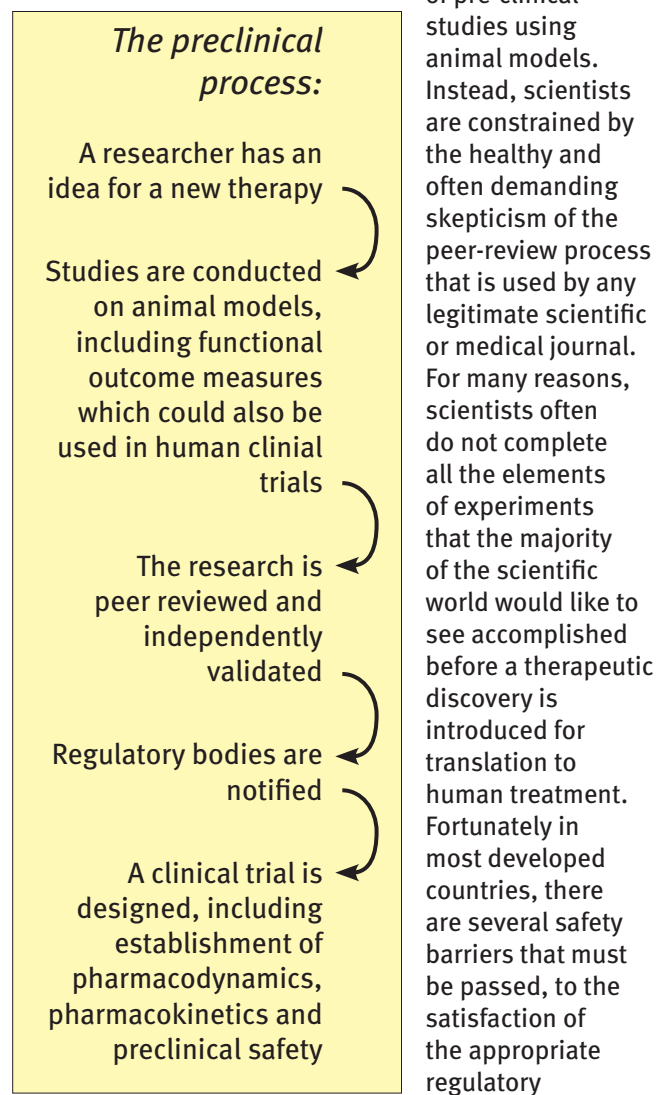
Here is a desired validation pathway for any pre-clinical discovery. The essential element is that the initial findings

> *The preclinical process:*
>
> A researcher has an idea for a new therapy
>
> Studies are conducted on animal models, including functional outcome measures which could also be used in human clinial trials
>
> The research is peer reviewed and independently validated
>
> Regulatory bodies are notified
>
> A clinical trial is designed, including establishment of pharmacodynamics, pharmacokinetics and preclinical safety

should be confirmed through independent studies by one or more groups of scientists. This validation of the original results may involve a complete replication of the initially reported experiment, but may also:

1. use slightly different types or variations on the experimental treatment for SCI, which would *demonstrate the robustness* of the finding. In short, after the therapeutic target has been initially identified, a number of different scientific techniques can be utilized to address it. Some or all of these complementary, but different approaches should provide similar results.

2. use different species, which would *demonstrate the fundamental nature* of the therapeutic target and/or intervention. There is divided opinion on whether primate (e.g. monkey) animal models must be completed prior to a clinical trial. However, most scientists would support the notion that more than one animal model of SCI (i.e. different animal species) should be completed prior to a clinical trial. Usually studies in two species are required for evaluation of the safety of a new treatment.

3. use the most clinically appropriate type of spinal injury to mimic the human condition, which would *demonstrate the relevance* of the discovery to possible human application. Increasingly, researchers are convinced that the pre-clinical efficacy should be established in a clinically relevant model of the human condition. In humans, the most common SCI is a contusion or compression type of injury. Thus, if the initial findings utilized a lacerating type of spinal injury (i.e. a cut spinal cord or use of an animal model with a minimal lesion of the cord), then a series of experiments examining the efficacy of the experimental treatment in a contusion type of spinal injury would also be desired.

Another important aspect of preclinical studies should be the inclusion of a "functional" outcome measure that is similar to one which could be used in a human clinical trial. In other words, anatomical evidence of neuronal repair is enticing, but insufficient. If a clinical trial fails to demonstrate a clinical benefit, it is important to know whether this is because the clinical assessment used an outcome measure which was not able to detect a subtle functional change or whether the treatment simply did not work in humans. Having comparable and validated outcome measures at both the pre-clinical and clinical level of study would make a stronger case that the experimental treatment had been tested fairly, but was not effective in humans, as it may have been in an animal.

Of course, you may logically ask, "Why are preclinical results not always independently replicated and validated before going to a clinical trial?" There are many explanations, including:

1. There is little incentive to replicate another person's

findings, because:

- little credit goes to an investigator for being "second"
- failure to replicate the initial finding is often claimed to be due to differences in methodology by the original authors.

2. There is no appetite by any government regulatory agencies to validate or regulate discoveries at the preclinical stage (e.g. FDA mandate is to protect people, not validate science). Thus, there is no enforcement of preclinical findings and it is unlikely to ever be coordinated on a worldwide basis.

3. In the case of commercially-sponsored research, the therapeutic compound under investigation may not be freely available to other scientists. Because of the high costs of failed clinical development programs, commercial enterprises are usually most careful about replicating their results before proceeding. However, they are often reluctant to allow research to be done out of their control, particularly because of the potential loss of related intellectual property (i.e. patents).

4. Without patent protection, many potential therapies have little chance of being taken forward to clinical development. The development and validation of a drug for clinical use can exceed $500 million dollars!

5. Other approaches--particularly surgical interventions--that are not highly regulated may proceed to clinical studies in the hands of "enthusiasts" who may be too impatient to carry out more animal studies.

For the sake of discussion, let's say the pre-clinical scientific finding has been independently replicated. What should happen now? Well, there are a number of important details that need to be established. For example, some of the more prominent issues are:

1. The appropriate regulatory agency (such as the FDA in the United States) should be contacted so there is an understanding of the requirements for moving towards a human trial.

2. The route for delivering the treatment to the patient (the effective clinical method for administering the drug or cells) needs to be established. For example, will it involve transplantation of cells directly into the spinal tissue, on top of the cord, or into the bloodstream? Does the experimental drug need to be infused into the spinal cord, on top of the cord, intravenously, or provided as an oral medication? The more invasive the route of administration, the greater the risks to the patient (e.g. risk of infection).

3. The timing of the experimental treatment (the effective "window of opportunity") needs to be identified. Can the treatment be provided at any time or does it need to be administered within a defined time window after SCI?

4. A facility needs to be established for the safe and consistent production of the precise formulation of the experimental drug, device or cell. There are very detailed regulations that apply to such a facility, known as Good Manufacturing Practices (GMP) which are issued by the regulatory agencies. The fundamental characteristic of these regulations is that every ingredient, process, procedure and piece of equipment used in the trial procedures is rigorously evaluated, documented and not allowed to change without equivalent levels of testing, evaluation and documentation.

5. Based on continuing animal studies, the pharmacodynamics and the pharmacokinetics of the drug or cell must be established, including dose-response relationships and the necessary scaling up of the presumed effective dose for human use.

6. The preclinical safety (with hopefully some additional efficacy) of the treatment in non-rodent animal species must be independently established, often by a contract research organization (CRO), which operates under another set of strict guidelines for validation and documentation of methods, known as Good Laboratory Practices (GLP). These studies would include a series of screens to establish that the experimental treatment does not cause adverse side-effects at the intended doses and durations of treatment, usually by testing much higher doses and longer treatments to explore the limits of tolerability.

By now, you might be thinking this is a very involved and demanding development process. It should be. The treatments we are considering could have dire consequences for people if they are not completed in a stringent manner.

5 What is ethical and unethical in the conduct of a clinical trial and what is informed consent?

Ethical obligations: The value of any research, including SCI research, depends in part on the ethical design and conduct of the research studies. A study involving risk to human subjects cannot be ethically defensible if it is not scientifically defensible. We all have an interest in the ethics of research investigations, including the obligation to protect the individual's rights and to minimize harm, as well as maximize benefit. It is also in everyone's interest to avoid any compromise of the ethical conduct of a clinical trial that would result in the necessity to question any findings. Unethical and poorly designed trials can lead to tremendous costs in terms of time, money, and most importantly the potential for injury or lost opportunities among those who are the study subjects. For these reasons, most researchers in the world adhere to well established principles for the ethical conduct of human research.

Any human clinical trial must, at a minimum, adhere to the international guidelines of the Declaration of Helsinki[24] and the standards of the host country, such as the Belmont report in USA.[25] Where standards come into conflict, it is the responsibility of the investigators to work with review committees and regulatory agencies to determine how best, if at all, the study can proceed.

One ethical point, sometimes overlooked, is that principal investigators leading a clinical trial are not allowed to accept payment for the treatment being tested, nor are subjects to be charged for their participation. This rule is in place to limit an investigator from biasing the outcomes of a clinical trial to find a benefit for a therapy where none actually exists. If a clinician or surgeon charged a patient to receive treatment with an experimental therapy that had yet to be validated or approved for clinical use, this would be viewed by the scientific community as not an ethical clinical trial. By definition, a clinical trial is conducted because we do not know whether the experimental treatment will be effective or safe. It would be unethical to charge someone for their willingness to assume the possible risks of participating in such a human study.

Good clinical trials are designed to avoid or minimize

> *It is essential that clinical trials be conducted ethically:*
>
> • researchers should not receive payment for testing treatments, and subjects should not be asked to pay to participate in trials;
>
> • trials should be designed to yield useful conclusions;
>
> • potential benefits should not be exaggerated.

potential confusion from a wide variety of factors that could make the outcomes of the treatment unclear. A clinical trial must be conducted in a manner that is likely to produce interpretable and useful information about whether a new treatment is or is not safe and effective. Trials that yield no useful conclusions are costly to the SCI community and society, as a whole.

It is important that subjects considering enrolling in a clinical trial understand that they are consenting to a purely experimental procedure that is of unknown benefit, and which could even cause serious adverse events including worsening of neurological function or death.

Potential benefits of a clinical trial should not be exaggerated. All participants in a clinical trial will receive the current standard of care, but in later stage trials, only some of the subjects will receive the experimental treatment that is being tested. To be sure that even a small improvement is detected, most clinical trials must compare the effects of a current treatment to the effects of the current treatment plus the experimental treatment. The alternative to the experimental treatment is often called a placebo treatment. The group of subjects receiving the placebo treatment is known as the "control" group, and while they will not directly benefit from any possible improvements, they will also not have the risks of any unexpected problems that might occur with the experimental approach.

It must also be remembered that it is relatively easy to get positive responses from subjects in a trial when they know they have been treated with an experimental therapy and when they expect or hope for a benefit. This is an example of a "placebo effect."

Even research investigators are not immune from the risk of bias, because of their hope to find something that is effective. To reduce the possibility of bias in the outcome of a trial, ethical and valid clinical trials usually assign subjects to either the experimental or control group of the study in a random manner. Ideally, neither the investigator nor subject should know which group the subject has been assigned until after the study has been completed

and analyzed. In short, everyone is blinded with regards to which treatment was provided to which subject.

Assessments for any changes in a subject's capabilities are also done in a blinded fashion, usually by a highly trained clinical evaluator (usually not the principal investigator) who is unaware and does not ask whether the subject has received the experimental or placebo control treatment. These are key rules for a credible clinical trial and are necessary standards to remove both subject and investigator bias. Such a trial is known as an RCT (randomized control trial) and is the late stage (e.g. Phase 2 or 3) trial design most often used to determine whether an experimental treatment has a functional benefit

Before you agree to participate in a clinical trial, you must understand all the potential risks involved in the experimental treatment. This is known as "informed consent."

When a clinical trial is conducted to test an experimental treatment that involves a surgical procedure, it is often desired that the results be compared with subjects who received a placebo or sham surgery. This is to rule out the possible benefit of the surgery alone. Should there be medical, ethical or legal reasons for not undertaking a sham surgical procedure, then appropriate control subjects should be presented for assessment in such a fashion that the evaluator cannot distinguish a subject from the experimental group from a participant within the control group, perhaps using such techniques as identical bandaging of the overlying skin. Of course, the control subjects would know they are not part of the experimental treatment group, but they must not divulge this to the evaluators or it could bias the accurate interpretation of the effects for the experimental treatment.

Research studies should proceed only if they are adequately designed to yield interpretable information regarding the objective benefit or lack of benefit of an experimental treatment. Therefore, the trial should include appropriate control groups, accurate and sensitive outcome measures, objective data collection and analysis, blinded analysis (whenever possible), and extended follow-up assessments over a time period sufficient to draw clear conclusions.

Numerous guidelines for the general conduct of any and all clinical trials have been developed and readers are encouraged to make themselves familiar with these teachings, especially those developed by the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use.[26] The United States FDA website also provides its guidelines and those of the ICH at its website.[27]

Informed consent: some individuals faced with the disability caused by SCI may choose to receive an experimental treatment or enter a clinical trial, not because they have weighed the potential risks against a small chance of benefit, but because their desperation leads them to disregard anything other than the possibility of a beneficial outcome. This situation places a high ethical obligation on clinical investigators to explain all possible outcomes to potential research subjects.

You need to have sufficient information in order to decide whether or not to participate in a clinical trial. This includes an understanding that you may be assigned to the control group (in other words, you would not receive the new treatment) or you may be assigned to the experimental treatment group, for which the researchers remain uncertain about its safety and/or potential benefits. This is a minimal expectation for any research study, but the standards for informed consent must be higher than normal for a project that requires sham surgery on the central nervous system (CNS).

There are many points that should be made clear to a person considering participation in a clinical trial. These include, but are not limited to, making clear to every potential subject that:

1. an experimental intervention is research, not therapy, and the reason for conducting the study is to determine whether or not it is safe and/or beneficial;
2. the current standard of treatment for SCI will be provided regardless of the subject's decision to participate in the research study; and
3. participation is always voluntary, and the subject can withdraw at any time for any reason.

An important part of that process is to clearly convey the probable and possible harm to someone who agrees to be a research subject. The following are examples of risks that should be explained in informed consent documents for SCI clinical trials.

- **Risk of pain:** therapies that aim to improve the growth of injured connections in the spinal cord could possibly also stimulate the growth of damaged pain fibers or sprouting from undamaged pathways, resulting in heightened pain that may be permanent or poorly responsive to therapy.
- **Risk of spasticity, dysreflexia:** therapies that aim to improve the growth of injured connections in the spinal cord could possibly also stimulate the growth of any fiber type in the spinal cord, resulting in an unknown spectrum of side effects including worsened spasticity or increased autonomic

dysreflexia, which is a syndrome of elevated blood pressure that can be dangerous or fatal (if untreated).

- **Risk of loss of function:** there is a possibility that the experimental therapy will improve function, cause no change in function, or cause a minor or a major loss of function, possibly including segments of the spinal cord that are currently unaffected by your injury.
- **Uncertainty of adverse effects:** because this is an experimental procedure, there may be risks that are currently unforeseeable. You will be informed of any significant new findings regarding the potential of adverse events in this trial.

- **Risk of infection:** any invasive procedure carries the potential risk of infection, particularly implantation of cells that are not fully sterilized prior to implantation. Cellular therapies may also require the administration of immunosuppressive agents, rendering subjects less resistant to infections such as pneumonia or urinary tract infections.
- **Burden on participating subjects:** while not usually a direct risk to your health, you should consider the various demands of the trial, such as the amount of time you may have to commit for the necessary assessments over the duration of the trial. You will then be able to decide if the burden is such that you do not want or will not be able to fully participate until the end of the trial.

6 What can jeopardize the accurate interpretation of the outcomes for a clinical trial and what can be done to prevent this from happening?

The short answer is there is an almost infinite number of ways bias can confound a clinical trial. The longer answer is there is an almost infinite number of ways bias can confound a clinical trial, including the following possibilities:

1. An investigator who knows the type of treatment the subject has received could knowingly or unknowingly bias the measured outcome in favor of a desired result, especially when there are no appropriate control subjects in the study. Clinical investigators are human and we all have a bias when it comes to our life's work!
2. Likewise, if a person living with SCI has paid for a treatment either with money or their physical and emotional involvement, it is likely they will wish to see and report a benefit, even if there is no objective, measurable data to support such a claim (the placebo effect). In the more extreme situations, when an experimental treatment costs tens of thousands of dollars or the entire community has helped pay for the procedure, there is a natural tendency to report a benefit so everyone can feel their support was worthwhile.
3. The very act of looking for a therapeutic benefit can lead to the perception of something positive, even if it is not due to the presumed treatment, often termed a false positive outcome.

All of these situations are a form of bias, and are some of the reasons that clinical trials are designed to avoid such confounding influences (see Section 4).

Because some people living with SCI will improve or deteriorate without any treatment (fig.3), we will never be able to accurately conclude whether the experimental treatment under study is beneficial or detrimental to the patient without including appropriate control subjects in a clinical trial. It is not sufficient to rely on historical control data, because conditions change with time and the control subjects from a previous trial may have been diagnosed, treated, or assessed differently than patients at the present time. Without appropriate controls, we learn little and without controls, we do not have a definitive trial of efficacy, nor is the treatment likely to be approved as a valid clinical therapy by a government regulatory body.

Control subjects should closely match the experimental subjects in as many ways as possible. Here are just a few more examples of confounding factors that should be randomly and equally distributed between the experimental and control groups: age, sex, other medications or damage to other organs, severity of SCI, level of spinal damage, surgical history, and rehabilitation history.

Thus, it is generally agreed that the clearest and most reliable information regarding the actual value of a potential therapy requires the analysis of some type of control group, the blinding of the subject to the identity of their treatment group, and assessments by a blinded evaluator over a sufficiently long recovery period (for acute SCI treatments this often means over at least a year) to ensure that any alteration in outcome is an enduring change. For example, it is possible that a simple surgical procedure itself, independent of any injected test substance or transplanted cell, may improve outcomes after SCI. This could be a consequence of surgery relieving pressure or tension on the spinal cord, improving the circulation of blood or cerebrospinal fluid, or other factors, including the potentially powerful effects of subject and investigator expectation about desired outcomes and benefits.

The choice of an appropriately matched control group and the ability to perform double-blinded analyses is not always a straightforward issue in SCI. For example, it is not difficult to include a control group when the substance under investigation is an orally administered drug with a relatively safe adverse event profile. In this case, a placebo-control arm is straightforward to include in the study, and double blinding can be implemented.

When the study requires open surgical manipulation, then the use of a sham surgery control group may subject a patient to risk of adverse events caused by the sham procedure itself. SCI patients may be medically unstable, concurrently infected, or at high risk of suffering post-operative complications such as pneumonia or other infection. Sham surgical procedures could also lead to autonomic dysreflexia. These risks are not trivial, and are particularly notable after acute SCI.

However, these risks may be made more acceptable by the value to be gained for science and medicine in a clinical trial that will yield a clear and statistically interpretable outcome.[19] Under these circumstances, an experimental SCI trial could be of benefit to society,

To reduce the potential for bias in a clinical trial, the trial should include a control group, subjects should not know to which treatment group they've been assigned, and results should be assessed by a blinded evaluator over an appropriate time period.

even if the subjects do not directly benefit. It should be remembered that the subjects who receive the experimental treatment are exposed to even greater risks with the possibility that they will gain no functional benefit. Discussions in the medical literature generally support the inclusion of control groups in clinical trials, even when these control procedures could represent some risk to the subject's health.[29]

Indeed, the consequences to humanity of allowing invasive surgical procedures without the adequate study of control groups has, in other medical conditions, led to countless unnecessary surgeries and their associated risks.[2] Examples of ineffective surgical procedures include mammillary artery bypass for ischemic heart disease and extracranial-to-intracranial artery bypass procedures for cerebral ischemia.[31][32] There is a real risk that a surgical intervention without real benefit for SCI could gain wide acceptance and implementation due to the lack of performance of a clearly interpretable clinical trial. In such a case, hundreds of thousands of SCI patients could subsequently be exposed to unnecessary surgical procedures that in some proportion of patients would lead to medical complications, potentially worsening their disability or even leading to death.

Even though the research investigators and ethics review committees might conclude that such research is acceptable, it ultimately must be up to individual research subjects to decide whether they perceive their personal risks to be justified by the possible benefits to society. The burden is on investigators to ensure that potential subjects will be enrolled only after they clearly understand and accept the uncertainty of any possible benefit, the nature of possible risks for participating in the research study, and the possibility of being assigned to the control group. This is a minimal expectation for any research study, but the standards for informed consent must be higher than normal for a project that involves a direct intervention into the central nervous system (see Section 5).

7 How are functional benefits of an experimental treatment measured for SCI?

Sensitive and accurate outcome measures are critical in designing useful SCI therapeutic clinical trials and objectively validating or invalidating a potential beneficial treatment. Different clinical targets such as tactile sensation, movement, autonomic function, personal capacity, performance, or community participation, normally require distinct and appropriate ways to measure an outcome (often called assessment tools). Different Phases of clinical trials also have different objectives and therefore require different outcome measurement tools. In brief, Phase 1 focuses on safety, Phase 2 on functional activity, and Phase 3 is the definitive or pivotal trial where clinically functional benefit must be demonstrated.[2] Assessment methodologies (i.e. tools) for evaluating a clinical endpoint of an SCI trial fall into three main categories:

1. Assessments aimed at describing the neurological connections to and within the spinal cord, regardless of the ability of the patient to functionally use those connections in an everyday activity. The ASIA scale is an example of such an assessment. This would also include assessments of neurological capacity that measure the activity or anatomy of the central nervous system, such as electrophysiological recordings or imaging assessments. When these outcome tools can be shown to accurately predict the long term functional benefits (or, clinical endpoints) resulting from a therapeutic intervention, they can also be thought of as surrogate endpoints. Once validated, surrogate endpoints can then be used in Phase 2 trials to evaluate early indications for the activity of an experimental treatment.

2. Assessments of the abilities of a patient with SCI to perform activities associated with everyday life. Examples are the Functional Independence Measure (FIM) and the Spinal Cord Independence Measure (SCIM). Such evaluations more directly measure clinically meaningful changes in the functional capacity of a study subject, but the changes in functional outcomes may not always be the result of a demonstrated change in spinal neurological activity or connectivity. Instead, any change in a person's functional capacity after SCI may be due to adaptive or compensatory changes within and/or without the central nervous system (CNS), including environmental accommodations and/or alternative strategies.

3. Assessments of an individual's level of participation in societal activities, or "Quality of Life" (QoL). QoL can be defined as a person's perception of their situation or position in life, within the context of both their personal and their society's values and culture, and relates to their personal concerns, standards and goals. The Short Form 12 or 36 Item medical outcomes health survey (SF-12 and SF-36) are examples of a health and QoL survey. This is a generic measure, as opposed to one that targets a specific age, disease, or treatment group.

The efficacy of experimental treatments can be measured according to improvements in neurological function, functional capacity, and quality of life.

Considerations for the use of the ASIA scale to measure a change in neurological function

There has been debate about how soon after acute SCI the ASIA examination can provide useful predictions about the eventual degree of impairment. It has been suggested that an ASIA assessment within the first 24 hours may not provide an accurate prognosis and that a later examination at 72 hours is a more reliable indicator, as the patient is medically more stable.[31][32] At later time points (greater than 12 months after SCI), the ASIA assessment may not capture the most important aspects of any functional change, since it was not meant to assess activities of daily living. Functional tests (see below) are perhaps more useful primary outcome tools for chronic studies.

Regardless of these concerns, it is essential that steps should be taken to standardize and optimize the accuracy of the ASIA assessment. For all patients being considered for entry into a trial, the clinical trial center(s) must conduct an independent and blind ASIA assessment just prior to the participant being randomly assigned to the therapeutic intervention or relevant control group. Subsequent follow-up ASIA assessments should also be undertaken at relevant time points over the course of recovery, as defined for that trial (e.g. first few weeks, first couple of months, and then at fixed intervals throughout the duration of the study) in the same blinded fashion, and preferably by the same examiner. In the absence of a more sensitive and accurate outcome tool, at least these ASIA assessments enable us to follow any initial detriments or benefits of a candidate therapy.

As valuable as the current ASIA Impairment Scale has been to the <u>diagnosis</u> of the severity and level of SCI, every measure has its limits in terms of sensitivity and accuracy. Since the ASIA scale only has 5 grades (A-E), it may not be sensitive enough to detect a small or subtle therapeutic effect. Only an experimental treatment with a very large effect could be validated with such an outcome measure or clinical endpoint. However, an intervention with a potentially smaller result might require a more sensitive outcome measure, such as a statistically significant change in the <u>ASIA motor score</u> (an ASIA sub-score, see fig.2)[2], which is a hundred point scale. Ten different muscle groups are assessed on each side of the body, each representing the functional motor state for a different level of the spinal cord. The strength of each muscle's contraction is scored on a 5 point scale as the individual attempts to initiate a voluntary movement which involves that particular muscle group.

In general, establishing a functionally meaningful ASIA motor score threshold to document the benefit of a therapeutic intervention depends on both the level and severity of the SCI, as well as the degree of spontaneous change in the motor score (throughout the period of the trial). For example, previous studies have indicated that a low-cervical, ASIA A injured patient is likely to show a spontaneous improvement of about 10 ASIA motor points during the first year after SCI. Therefore, to demonstrate the efficacy of a therapeutic intervention, a response to the treatment of an additional 10 point improvement in the ASIA motor score (efficacy threshold now being 20 points) might be considered a statistically valid primary outcome threshold, when compared to an appropriate control population.[1]

Different thresholds need to be specified for a response at each level and severity of SCI. For example, the spontaneous recovery of ASIA B cervical patients one year after a cervical SCI has been reported to be about 30 (out of the 100) motor points. Thus, demonstration of a therapeutic benefit might require an additional 20 point improvement to indicate a functional benefit. It should be noted that the absolute difference in the number of ASIA motor points between an experimental and appropriately matched control group is not as important as a statistically valid difference between the experimental and control groups and whether that difference confers an improved functional outcome to the person with SCI.

Finally, several studies have reported a substantial (25-50) motor point improvement during the first year after SCI for people with ASIA C and D classifications, which is on top of their initially high ASIA motor score. This creates a "ceiling effect" that may make it difficult

Efficacy can be measured using the ASIA scale, electrial recording techniques and functional testing.

to discriminate a statistical difference between the ASIA motor scores of SCI participants in the experimental and control arms of a study. In short, a treatment effect would not be detectable. Therefore, a functional test (see below) may be a more appropriate primary outcome tool for ASIA C and ASIA D trial participants.

Statistically speaking, the use of ASIA motor scores as a primary outcome endpoint is perhaps most useful for SCI subjects initially enrolled in a clinical trial as either ASIA A or ASIA B. The obvious drawback with this suggestion is ASIA A and ASIA B subjects initially have motor-complete spinal injuries and it may be difficult to produce or discern a clinically meaningful improvement in their subsequent ASIA motor score. If the ASIA scale measurements are somewhat limited in their sensitivity and accuracy for discerning whether a treatment has a significant benefit, then what other outcome measurement tools might be used?

Other tools for measuring a change in neurological function after experimental treatment of SCI

Electrical recording techniques such as <u>somatosensory evoked potential (SSEP)</u>, <u>electromyographic (EMG)</u> and <u>motor evoked potential (MEP)</u> recordings can provide objective data such as the speed and strength of neural signals to assess preserved or recovering spinal connections. These quantitative signals can be analyzed by a blinded investigator. Furthermore, electrophysiological recordings have the advantage that they can be performed on comatose or otherwise unresponsive subjects. EMG recordings are useful in the assessment of function, both in response to voluntary effort and when combined with electrical or magnetic stimulation of peripheral nerves (reflexes) or motor cortex (i.e. MEP). These technologies complement the ASIA neurological assessment, and a combination of SSEP, MEP and/or EMG measurements provides information about spinal cord function that is not retrievable by other clinical means and may have additional value in predicting functional outcomes.[33] [34]

Non-invasive imaging, such as magnetic resonance imaging (MRI) has become a cornerstone for detecting the location (and to some degree the severity) of an acute SCI, as well as detecting possible complications arising during chronic SCI. MRI, along with Computerized axial Tomography (CT) and x-ray images, are useful diagnostic tools and potentially helpful for screening participants to be included or excluded from a clinical trial. MRI has been useful in determining the extent of cord compression, outlining hemorrhages and <u>edema</u> after human spinal injury and in the near future, might be useful in monitoring regressive or progressive

changes in spinal cord tracts.[35][36][37][38] With further development, MR technologies may provide a useful early measure that would accurately predict the longer term functional benefits of an experimental intervention after SCI.[38]

Functional tests

A measurable improvement in the performance of a meaningful function, behavior, or activity of daily living (ADL) is absolutely necessary for any therapeutic intervention to be universally accepted as beneficial. Accurate and sensitive functional outcome measures are therefore critical to SCI clinical trials and this will be especially true for any Phase 3 studies.

It has been suggested that the Functional Independence Measure (FIM) scale is a general disability scale, which is not specific for SCI and therefore may not be the most suitable scale for assessing functional changes after SCI. The recently developed Spinal Cord Independence Measure (SCIM) assessment may be a more specific and accurate outcome tool for detecting clinical endpoints in SCI.[39][40][41] The continued development and validation of tests that quantify highly relevant behaviors such as walking or hand function are most important; such tools may have greater utility for documenting the subtle benefit of an experimental treatment than a more global scale of disability.

For clinical trials involving people with motor-incomplete SCI (ASIA C and ASIA D), several validated tests of balance and ambulatory performance have been developed, including the Walking Index for Spinal Cord Injury (WISCI) and a number of timed walking tests.[42][43] WISCI is a 21-level hierarchical scale of walking based on physical assistance and the need for braces and devices, with a range from 0 (unable to walk) to 20 (walking without assistance for at least 10m). It is an example of a sensitive scale for rating a specific functional activity in people with incomplete SCI. WISCI is currently a valid

A measurable improvement in the performance of a meaningful function, behavior, or activity of daily living is absolutely necessary for any therapeutic intervention to be universally accepted as beneficial.

outcome measure for strategies directed to improve ambulation by subjects with incomplete SCI.[42] A more accurate assessment may be provided by a combination of WISCI plus some of the more quantitative timed walking tests.

The number of people surviving with a cervical level spinal injury has risen dramatically over the past few decades and cervical SCI now accounts for approximately 50% of all people living with a SCI. Validating a functional outcome tool to assess arm and hand capacity after a cervical spinal injury has therefore been identified as a top priority. There is currently a lack of agreement on what might be the most useful test of arm and hand function after SCI. Many of the scales developed have been deemed too insensitive to track small but potentially meaningful functional gains. The majority of tests have been developed within the domains of stroke or hand surgery, but less often to describe the impairment and course of hand function recovery after SCI. An initiative is now underway across Canada, the United States, and Europe to develop an integrated hand function test as a valid assessment tool for SCI clinical trials.

Improvement of functional abilities, reflected in activities of daily living will be the most meaningful and valued outcomes. However, the early phase clinical trials for drug therapies (Phase 1 and 2) completed to date have focused on assessment of neurological connectivity to provide "proof of principle" measures. It is likely that these neurological assessments will continue to be used as outcome measures. However, no experimental intervention will be considered effective for the treatment of people living with SCI unless it improves their ability to function and engage in everyday life within their society. Outcome assessment tools that accurately and sensitively demonstrate such benefits will need to be incorporated into the more definitive and confirmatory Phase 3 clinical trials.

8 If you participate in a clinical trial, how does it affect your participation in future SCI clinical trials?

The answer to this important question depends on the overlap in the mechanism of action for the experimental treatments used in each of the successive trials and the time span between the trials. Simply speaking, if the two different trials involve an investigation of similar experimental drugs or drugs with similar cellular mechanisms, it is possible that you will be excluded from participating in the second trial, regardless of whether the first experimental drug had a detectable functional benefit or not. The reason for this is that the first experimental drug may have had some very subtle or residual effect that was undetected by the outcome measure used in the previous trial, but could enhance or negate the effects of the experimental drug in the second trial. In short, the possibility of drug interactions is a potential confounding factor for the accurate interpretation of the results in the second trial and thus an investigator may disallow the participation of a subject who has already participated in a similar clinical trial.

Depending on the therapy being evaluated, it is possible that your participation in one clinical trial could make you ineligible to participate in a later trial

A similar logic would also apply to cell transplants into the injured spinal cord. Currently, there are no acceptable methods for tracking the fate of transplanted cells. Will the transplanted cells survive? Will they migrate to appropriate locations within the cord? Will they multiply? What will they become after transplantation? Will they stay relatively immature or become a neuron, a glial cell, or even a cancer cell? Since we currently have no reliable and/or acceptable technologies for following the fate of transplanted cells, it makes it difficult for any investigator to rule out the possibility that the cellular or surgical effects of a previous transplantation would not have an effect on the outcomes from a second transplantation or a second trial involving a therapeutic drug; thus there is sufficient reason to exclude such an individual from the second trial.

In the future, there may be ways to clearly demonstrate that a previous clinical trial experience will not confound or influence the outcomes of a second trial. However, the final decision will still be influenced by the similarities in the treatment actions between the two trials.

Another influence on whether a previous trial experience would exclude someone from a second trial is the time since the previous trial. The longer the time between the two trials, the less concern there may be. This would especially apply to a previous drug treatment where the effect of the drug is not expected to persist for a long period of time (see pharmacokinetics discussion in Section 4).

Subjects who participate in a clinical trial and later find out that they were assigned to the control group might be concerned about whether this will disqualify them from participating in a second trial or receiving an approved treatment later. The answer is more than likely that they will be eligible. This should be true, unless there is a limited time for the use of the treatment after SCI which has now been exceeded. Finally, it should be remembered that if any treatment has been validated in a trial program and approved for clinical use of a spinal injury similar to theirs, then they are likely to receive the therapy regardless of their participation in a previous clinical study.

9 What are some of the current experimental treatments proposed for SCI and at what stage are they in terms of their validation as beneficial?

With all that has been discussed so far, what is the current state of experimental treatments for SCI? Potential therapeutic interventions after SCI fall into one or more of several general categories:

• neuroprotection
• repair / regeneration
• plasticity enhancing
• replace / assist function

Interventions with growing validity: Historically, there are very few surgical or therapy programs that have been validated for the care and treatment of SCI. Worldwide, there is developing consensus that early surgical decompression of the compressed or contused (bruised) spinal cord is often necessary and recommended. This can be achieved in two general ways.

First, a misaligned spinal column, which is causing

undue pressure on the spinal cord, can often be brought into better alignment with the use of some form of traction. Therapeutic spinal traction uses manually or mechanically created forces to stretch and mobilize the spine, based on the application of a force (usually a weight) along the longitudinal axis of the spinal column.

Second, most clinical practitioners agree that fractures of the vertebral spinal column should be stabilized through the insertion of rods and screws to properly align the vertebral column or fuse adjacent vertebrae to strengthen the vertebra, promote bone re-growth, and reduce the likelihood of further spinal cord injury in the future.

There has been some question as to how soon these surgical procedures should be completed after SCI and this is the subject of an ongoing clinical study in North America called STASCIS (Surgical Treatment for Acute Spinal Cord Injury Study). Until this study is complete, patients with SCI should undergo appropriate operative procedures when they are medically fit to withstand the surgical procedures and where there is clear anatomical and neurological evidence that the spinal cord has been compressed and/or the vertebral column is damaged and unstable.

There is also emerging consensus that *active* rehabilitation after SCI is important and effective in preserving any residual body functions, as well as improving the recovery of functions after SCI. By *active* rehabilitation, we mean activities that involve the individual contributing their voluntary efforts to the performance of the task. Passive rehabilitation therapy might include massage and the movement of an individual's limbs through the entire range of motion normal for that limb. Passive rehabilitation is an essential part of any treatment protocol, but is unlikely to be sufficient to maximize functional outcomes after SCI. To date, however, no specific active rehabilitation therapy has been completely validated as essential or effective for functional recovery after all the different types of SCI.

Once again, if an individual is medically stable and will not suffer any detrimental effects due to the movements associated with physical rehabilitation activities, then rehabilitation training can be started soon after SCI.

Most spinal cord injuries are incomplete and often asymmetrical, which means there is some residual function below the level of spinal damage and it may not be equal on both sides of the body. This spared capability is often noted by retention of some sensory feeling (e.g. detection of a pin prick) or ability to move part of a limb (raise a shoulder, move a finger, or wiggle a toe). In an effort to maximize functional recovery after SCI, a variety of strategies have been developed to build upon and extend residual functions, including repetitive voluntary movement training, strength training, and constraint use therapy (e.g. where the better functioning arm is constrained to force the use of the weaker limb). Some muscle movements, such as hand function or diaphragm contractions (to power breathing) have been enhanced by functional electrical stimulation (FES) of specific nerves or muscles.

There are a large number of FES devices that have been developed. This booklet cannot adequately review the many issues associated with the most appropriate uses for these technologies; some recent review articles [47,48] will provide more in-depth information on this subject.

Active rehabilitation (physical, occupational, or psychosocial) is, and should always be, part of any therapy for improving outcomes after SCI. For a detailed discussion of published evidence of SCI rehab strategies and practices, please consult the SCIRE (Spinal Cord Injury Rehabilitation Evidence) report, which is available as a free download from the ICORD website at www.icord.org

Interventions that have yet to be validated

Over the past 2 decades, a small number of major SCI clinical trials have been undertaken and completed, including investigations of the neuroprotective benefits of Methylprednisolone,[16 17 44 45] GM-1 (Sygen),[18 19] and Gacyclidine (GK-11).[46] These trials were done in a highly valid and commendable manner and the data has been valuable for the design of current and future clinical trials. Unfortunately, none of these therapeutic interventions showed sufficient statistical evidence for efficacy to be approved for clinical use by a regulatory body, nor have they become widely adopted into worldwide clinical practice.

On the accompanying table are *some selected experimental approaches* for the treatment of SCI that have been or are being examined in late-stage pre-clinical or early clinical studies. This list is *not a complete or comprehensive list* of experimental approaches that have been proposed over the years, but gives the reader an idea of what types of investigations are being pursued. The interventions are categorized by what has been suggested to be their principal action. All of the data in this table is subject to change (and will change).

Selected experimental approaches for the treatment of SCI

Mechanism of Therapeutic Action	Name of Treatment	Pre-clinical Evidence from Multiple Studies (animal models of SCI)	Validated Clinically and Approved for Sale (appropriate trial procedures with human subjects)	Status of Clinical Trial	Clinical Use for SCI
Neuroprotective (also see repair /regeneration)	Methylprednisolone sodium succinate (MPSS), an anti-inflammatory corticosteroid	Good, with only a few inconsistencies in animal models of SCI	No, missed statistical significance, except for post-hoc statistical support	Completed[34]	Yes, in some, but not all, countries
	GM-1 (Sygen) a ganglioside found in neuronal cell membranes	Limited	No, missed statistical significance	Completed[35]	Rarely
	Thyrotropin Releasing Hormone	Good, but some inconsistencies in results from animal models of SCI	No	One small trial completed, but not replicated to date	
	GK-11 (Gacyclidine) a Glutamate (excitatory) amino acid antagonist	Good, but mainly cell culture studies; limited animal models of SCI	No, missed statistical significance, except for post-hoc statistical support	Phase 2 completed[36]	No
	Minocycline (Minocin) a tetracycline (antibiotic) and anti-inflammatory	Good, but some inconsistencies in results from animal models of SCI	Approved by several regulatory agencies for other use (e.g. acne)	Phase 2 underway in Canada	No
	Erythropoietin (EPO) a kidney hormone, increases red blood cells and anti-inflammatory	Limited, with some inconsistency in animal models	Approved for use for certain blood disorders such as anemia	Preclinical; no clinical trial (to date) for SCI	No
	Transplantation of cells that secrete growth (survival) factors	Limited, but growing body of evidence suggests potential benefits for CNS degenerative diseases where neurons have been lost	Not yet	Phase 1 studies undertaken in patients with Alzheimer's disease	No
Repair / Regeneration (may also promote neuroprotection and/ or plasticity)	Transplantation of autologous (patient's own) macrophages	Limited, controversial whether transplantation of activated macrophages are beneficial or harmful	Not yet	Phase 1 complete; Phase 2 study partially complete (on hold due to lack of funding)	No
	Transplantation of bone marrow stromal (stem) cells	Limited, still controversial as to what these cells will become after transplantation	Not yet	Phase 2 underway in Brazil	No

Selected experimental approaches for the treatment of SCI

Mechanism of Therapeutic Action	Name of Treatment	Pre-clinical Evidence from Multiple Studies (animal models of SCI)	Validated Clinically and Approved for Sale (appropriate trial procedures with human subjects)	Status of Clinical Trial	Clinical Use for SCI
Repair / Regeneration (con't)	Inosine, nucleoside and muscle purine nucleotide	Good	Not yet	Phase 2 trial underway for multiple sclerosis, but no clinical trial (to date) for SCI	No
	Cethrin (Rho antagonist; intracellular signaling pathway)	Good, with some inconsistencies in results from animal models of SCI	Not yet	Phase 1 complete (no reported toxicity)	No
	Rolipram an anti-depressant, interacts with c-AMP intracellular signaling pathway	Good	Approved for use in Japan and parts of Europe for depression	Several Phase 1 and Phase 2 trials for other disorders; none (to date) for SCI	No
	ATI-355 (NOGO) antibody that blocks inhibitory actions of CNS myelin	Good, strong evidence that CNS myelin inhibits axonal growth	Not yet	Phase 1 underway in Europe	No
	Chondroitinase, bacterial enzyme, degrades proteoglycans on glial astrocytes	Good, strong evidence that astrocytes after CNS injury are inhibitory to repair	Not yet	Preclinical; no clinical trial (to date) for SCI	No
	Transplantation of embryonic olfactory cortex cells	Limited, still controversial as to what is the fate of these cells after transplantation and whether they are beneficial	Not yet	No appropriate clinical trials (to date) such as randomized control trials	No, but patients can pay for treatment in China
	Transplantation of nasal olfactory ensheathing cells	Limited, still controversial as to whether they are beneficial	Not yet	Phase 1 trial completed in Portugal; Phase 1 underway in Australia	No, but patients have paid for treatment in Portugal

Selected experimental approaches for the treatment of SCI

Mechanism of Therapeutic Action	Name of Treatment	Pre-clinical Evidence from Multiple Studies (animal models of SCI)	Validated Clinically and Approved for Sale (appropriate trial procedures with human subjects)	Status of Clinical Trial	Clinical Use for SCI
Repair / Regeneration (con't)	Transplantation of Schwann cells	Good	Not yet	No	No
	Transplantation of human stem or progenitor cells (derived from embryonic or adult sources, including umbilical cord, neural tissue, etc.) (Also see above)	Limited, but very active area of preclinical scientific investigation; many critical scientific details still unknown (e.g. preferred type of cell for transplantation, survival, differentiation, and proliferation of cells, control of cell functions)	Not yet	No appropriate clinical trials (to date) such as randomized control trials, published as yet	No, but patients have paid for treatments in Russia and China
	Transplantation of peripheral nerve bridges	Good, but mainly limited to anatomical regrowth of some axons with little functional recovery observed	No	No appropriate clinical trials have been conducted. Most scientists agree that reconnection of spinal cord with peripheral nerve bridges alone is unlikely to yield therapeutic benefit.	No, but patients have paid for such treatments in Taiwan, and South America
CNS Plasticity Enhancing (also see repair / regeneration)	Active Rehabilitation	Very good evidence that activity or task-specific training can promote formation of new local CNS connections	Non-invasive rehabilitation strategies are rarely validated by regulatory agencies	Numerous clinical trials for other neurological disorders (e.g. Stroke)	Yes, especially for incomplete SCI
	Body Weight Support Treadmill Training	Very good evidence that this form of task-specific rehabilitation improves outcomes after SCI (especially incomplete SCI)	Not yet	Phase 2 multicenter study found no statistical benefit over other forms of active rehab.; other studies underway	Yes, especially for incomplete SCI

Selected experimental approaches for the treatment of SCI

Mechanism of Therapeutic Action	Name of Treatment	Pre-clinical Evidence from Multiple Studies (animal models of SCI)	Validated Clinically and Approved for Sale (appropriate trial procedures with human subjects)	Status of Clinical Trial	Clinical Use for SCI
Replace or Assist Function (Note: may also promote plasticity)	Functional Electrical Stimulation (FES) has a number of applications to assist a variety of functional impairments. Varieties of specific devices have and are being developed. The effectiveness of any device often depends on how closely the technology matches the individual's specific disability.	The published data supporting the use of these devices is beyond the scope of this review. More information is available in published review articles[47,48]			
	Functional Electrical Stimulation (FES) of phrenic nerve (to assist breathing)	Good	Yes, but often for very restricted applications	Several small trials completed	Yes, in a small number of patients with high cervical injuries and intact phrenic nerve activity
	Functional Electrical Stimulation (FES) of sacral roots (to promote bladder and bowel function)	Good	Yes	Numerous small trials completed	Yes, in a small number of patients
	Functional Electrical Stimulation (FES) of limb muscles (to improve arm or hand function, as well as standing or walking)	Good	Yes, but often for very restricted applications	Several small trials completed	Yes, for specific conditions that will benefit from the technology
	Fampridine (4-aminopryrideine) improves conduction velocity in damaged (demyelinated) axonal fibers	Good, evidence of activity in two animal models of chronic SCI	No	Numerous trials, including a randomized control trial (RCT). Mixed results for various clinical endpoints. Currently in development for Multiple Sclerosis	Not approved, but some individual use
Alleviate Pain	Gabapentin	Good	Not specifically for SCI pain	Gabapentin to reduce neuropathic pain in chronic complete SCI; including a RCT study	Not approved, but some individual use

10 What should you ask before agreeing to take part in a clinical trial? *(your participation checklist)*

Here are some questions to pose to the researcher inviting you to participate in a human study. This checklist may assist you in your decision whether or not to participate.

1. Safety	Yes	No	Additional in-depth information
a. Are there safety risks associated with this experimental treatment?			
b. Could my condition or my health get worse after this experimental treatment?			
c. If so, can you describe the possible risks associated with this experimental treatment?			
2. Possible benefits			
a. Can you describe the possible specific benefits of this experimental treatment?			
b. Can you describe the maximum level of recovery I might see after this treatment?			
c. Can you describe how any potential benefit will be measured?			
d. Is this outcome measure accurate and sensitive as an assessment tool?			
3. Preclinical evidence			
a. Can you describe the preclinical evidence that demonstrates this experimental treatment is beneficial (i.e. in animals with SCI)?			
b. Have these findings been independently replicated?			
c. If they have been replicated, is there a consensus among the scientists that this treatment addresses a valid therapeutic target for improving my functional outcomes?			
d. Are there any dissenting opinions and do these arguments have some validity for not going forward with this treatment?			

4. Clinical trial protocol	Yes	No	Additional in-depth information
a. Is this human study registered as a clinical trial with an appropriate qualified regulatory body?			
b. Can you describe what clinical trial phase this particular human study falls within?			
c. Is there a control group in this study?			
d. Could I be randomly assigned to the control group?			
e. Can you tell me how long I will be assessed for any change in outcome?			
f. Will I be blinded to whether I have received the experimental or control treatment?			
g. Will the investigators and examiners be blind to what treatment I have received?			
5. Participation in Other Trials			
a. Will my participation in this clinical trial limit my participation in other SCI clinical trials?			
b. If I am assigned to the control group and the experimental treatment is subsequently validated as an effective therapy for my type of SCI by this clinical trial program, will I be eligible to receive this treatment later?			
6. Payments and costs			
a. Do I have to pay for this treatment?			
b. Are there any other costs associated with my participation in this study?			
c. Will my expenses associated with participating in this study be paid (e.g. travel to center for follow-up assessment)?			
7. Independent assessment of the treatment and investigator			
a. Can you provide me several names of scientists and clinicians (not involved with this study) who can provide me independent advice about this treatment and your reputation?			

So, what should the answers be?

So what do we, the authors, say should be the general answers to these questions? Please see below, but regardless of our opinion, it is a personal decision for which the individual living with SCI has to weigh the possible benefits against the possible risks in determining their course of action.

1. Safety

a. *Are there safety risks associated with this experimental treatment?*
Answer: should be YES; no one can guarantee total safety, but some information should be available about such risks from pre-clinical or earlier Phase clinical studies.

b. *Could my condition or my health get worse after this experimental treatment?*
Answer: should be YES again; if someone states there are little or no risks you should be wary.

c. *If so, can you describe the possible risks associated with this experimental treatment?*
Answer: the investigator should be able to discuss in detail the possible risks associated with this human study.

2. Possible benefits

a. *Can you describe the possible specific benefits of this experimental treatment?*
Answer: the investigator should describe a range of possible benefits ranging from very subtle to modest functional improvements.

b. *Can you describe the maximum level of recovery I might see after this treatment?*
Answer: anyone who claims you are going to make a dramatic recovery with the return of almost full function should be avoided as there is no evidence for any treatment having such striking outcomes, even in preclinical animal studies.

c. *Can you describe how any potential benefit will be measured?*
Answer: the investigator should be able to describe a number of different measures that will be used to evaluate your progress after treatment.

d. *Is this outcome measure accurate and sensitive as a tool?*
Answer: the investigator should be able to describe the strengths and limitations of the evaluation procedures; once again, nothing is perfect.

3. Preclinical evidence

a. *Can you describe the preclinical evidence that demonstrates this experimental treatment is beneficial (i.e. in animals with SCI)?*
Answer: the investigator should be able to outline the evidence, including the strengths and limitations of the treatment approach.

b. *Have these findings been independently replicated?*
Answer: this could go either way, but there should be evidence that other scientists have obtained similar results when investigating this therapeutic target or approach.

c. *If they have been replicated, is there a consensus among the scientists that this treatment addresses a valid therapeutic target for improving my functional outcomes?*
Answer: this could go either way, but there should be some published discussion (e.g. a review) suggesting that the experimental treatment you are considering could alter or effect a valid target for improving functional outcomes after SCI.

d. *Are there any dissenting opinions and do these arguments have some validity for not going forward with this treatment?*
Answers: the investigator should be able to provide you with a summary of the pros and cons for the treatment. If not, be wary of any treatment that is claimed to have no limitations; scientists are usually very critical of each other. Use the internet to look up the most recent publications on the proposed treatment (www.pubmed.gov is a good starting point). If you run into biological or medical terms that you don't understand, one of your health care providers should be able to help.

4. Clinical trial protocol

a. *Is this human study registered as a clinical trial with an appropriate, qualified regulatory body?*
Answer: should be YES and the investigator should be able to provide you the details immediately. If the answer is vague on this point, you should be wary.

b. *Can you describe what clinical trial phase this particular human study falls within (Phase 1, 2, or 3)?*
Answer: should be immediate and in as much detail as you want.

c. *Is there a control group in this study?*
Answer: should be YES. If not, then this should be a Phase 1 "open label" study (safety only). If not, then this human study is unlikely to be a clinical trial and you should be wary.

d. *Could I be randomly assigned to the control group?*
Answer: should be YES for Phase 3 trials, If not, then this is likely not a valid clinical trial.

e. *Can you tell me how long I will be assessed for any change in outcome?*
Answer: should be anywhere from a minimum of 6 months to a year after treatment. It is possible that you may have to initially commit several weeks and this may include hospital stay as an in-patient. Subsequently, you may be asked to return for assessments at defined time points throughout the

following months. Once you agree to participate, you should be willing to complete the full trial protocol, even if you feel that you are not benefiting. Participants who withdraw from a study undermine the completion of the trial in a timely fashion.

f. *Will I be blinded to whether I have received the experimental or control treatment?*
Answer: If at all physically possible, the answer should be YES. If not, it should be a Phase 1 trial. If not a Phase 1 trial then you should be wary that this is not a valid clinical trial. Sometimes you cannot help but know what group you are in, but you should be asked not to tell the examiners whether you are in the experimental or control group until the trial data is completely analyzed.

g. *Will the investigators and examiners be blind to what treatment I have received?*
Answer: this should be a definite YES, unless it is a Phase 1 trial. If not, it is not a valid clinical trial and you should be wary.

5. Participation in other trials

a. *Will my participation in this clinical trial limit my participation in other SCI clinical trials?*
Answer: should be YES, that this is a possibility. The investigator should be able to outline which type of trials you may be excluded from in the future.

b. *If I am assigned to the control group and the experimental treatment is subsequently validated as an effective therapy for my type of SCI by this clinical trial program, will I be eligible to receive this treatment later?*

Answer: should be YES, unless your SCI condition changed, or there was a limited time for treatment after SCI, which as now been exceeded. Generally, once an experimental treatment has been approved by a regulatory agency for clinical use you would be eligible for treatment.

6. Payments and costs

a. *Do I have to pay for this treatment?*
Answer: this should be NO. If Yes, then this is not a valid clinical trial and you should be wary.

b. *Are there any other costs associated with my participation in this study?*
Answer: you should not have to pay for any procedure specifically related to a clinical trial program, but you, or your health care insurance provider, may have to pay for the current standard of medical care.

c. *Will my expenses associated with participating in this study be paid (e.g. travel to center for follow-up assessment)?*
Answer: should be YES.

7. Independent assessment of the treatment and investigator

a. *Can you provide me several names of scientists and clinicians (not involved with this study) who can provide me independent advice about this treatment and your reputation?*
Answer: should be YES and you should be able to verify the credibility of the study and the credentials of the investigators easily and readily via the internet.

11 Glossary of selected terms

[page numbers indicate on which page the term is used first in this document; where there are no page numbers, the terms are commonly used in discussion of experimental treatment and are provided for your reference]

Activities of Daily Living (ADL): activities involved in self care, communication and mobility, such as dressing, eating, and other skills necessary for independent living. [p.22]

Ambulation: walking, with or without the use of assistive devices such as a walker or crutches [p.24].

ASIA (American Spinal Injury Association): a group of physicians and other medical professionals who treat SCI. For more information, see ASIA's website: www.asia-spinalinjury.org. [p.11]

ASIA Impairment Scale (AIS): describes the completeness or severity of a spinal injury. A booklet and training manual is available from ASIA that summarizes the AIS scale and clinical assessment protocol (www.asia-spinalinjury.org/publications/index.html) [p.11]

AISA A: no motor or sensory function at the level of S4-S5 sacral segments. Also known as AIS A

AISA B: some sensory function below the neurological level, including S4-5, but not motor function. Also known as AIS B

AISA C: some motor function below the neurological level, but more than half of the key muscles involved have a muscle strength score of less than 3, which is classified as non-functional (Fig. 1). Also known as AIS C

AISA D: motor function below the neurological level, but more than half of the key muscles have a muscle grade of 3 or more, which is classified as functional (Figure 1). Also known as AIS D

AISA E: normal motor and sensory function. Also known as AIS E

ASIA Assessments form the basis for the International Standards for Neurological and Functional Classification of Spinal Cord Injury (the ASIA International Standards). They are conducted on subjects lying on their backs, and involve a qualitative grading of sensory responses to touch and pin-prick at each of 28 dermatomes along each side of the body and a qualitative grading of the strength of contraction within 10 representative (key) muscles, primarily identified with a specific spinal level, 5 for the upper extremity (C5-T1) and 5 for the lower extremity (L2-S1) on each side of the body.

ASIA Motor Score: calculated by assigning to one muscle group, innervated and primarily identified with a specific spinal level, a score between 0 (no detectable contraction) and 5 (active movement and a full range of movement against maximum resistance). C5 to T1 and L2 to S1 are tested, giving 10 levels on each side of the body for a possible maximum score of 100. The Lower Extremity Motor Score (LEMS) is a maximal 50 point subset of the ASIA motor score for the representative leg and foot muscles. The Upper Extremity Motor Score (UEMS) is a maximal 50 point subset of the ASIA motor score for the representative arm and hand muscles.

Motor Level is defined as the most caudal (lowest) spinal level as indexed by the key muscle group for that level having a

muscle strength of 3 or above while the key muscle for the spinal segment above is normal (= 5) [p.23]

ASIA Sensory Score: calculated by testing a point on the dermatome for each spinal level from C2 to S4-5 for both light touch and pinprick sensation. Each point is assigned a score from 0 (absent sensation) through 1 (abnormal sensation) to 2 (normal sensation). This gives a possible maximum score of 56 on each side for a maximum total of 112 each for light touch and pinprick. Sensory Level: is defined as the spinal segment corresponding with the most caudal dermatome having a normal score of 2/2 for both pinprick and light touch. [p.11]

Assistive, Adaptive, Supportive, and Protective Devices: a variety of implements or equipment used to aid individuals in performing tasks or movements. [p.10]

Astrocytes: see Glia. [p.28]

Autonomic dysreflexia: An autonomic reflex causing a sudden, severe, increase in blood pressure in response to pain or discomfort, usually originating below the level of paralysis. Autonomic dysreflexia is an ongoing medical complication which occurs in people with spinal cord injury, most often with an injury at or above the 6th thoracic level of the spinal cord and usually no earlier than 4-6 months after injury. Tetraplegics are more prone to this complication as their autonomic nervous system is unable to oppose the reflex. Commonly caused by an over-full bladder or bowel it presents as profuse sweating, flushing and/or a blinding headache. It is a medical emergency, and if untreated can cause death. [p.19]

Balance: the ability of an individual to maintain the body in equilibrium with gravity both statically (e.g. while stationary) and dynamically (e.g. while walking). [p.24]

Belmont Report: a report created by the former United States Department of Health, Education, and Welfare (renamed the Department of Health and Human Services) entitled "Ethical Principles and Guidelines for the Protection of Human Subjects of Research." The text is available at: www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm (also see Helsinki Declaration) [p.18]

Bias: the tendency of any factors associated with the design, conduct, analysis and interpretation of the results of a clinical trial to make the estimate of a treatment effect (therapeutic benefit) that differs from its true value (for example, claim a benefit when no legitimate evidence exists). [p.15]

Blinded assessments: those evaluations conducted on a clinical trial subject where the evaluator does not know or ask whether the subject is part of the experimental or control group. Blinded assessments are considered important to reduce any bias in the analysis of the effects of an experimental treatment. There are different levels of blinding:

Single-blinded studies: either the clinical investigator or the subject, but not both, are blinded. [p.15]

Double blind studies: neither the participating trial subject nor the investigators, institutional staff or sponsoring company are aware of the treatment each subject has received during the trial. Ideal blinding would ensure that the treatments cannot be distinguished by subjective experience, appearance, timing, or delivery method by any of the subjects, investigators, research staff, or clinical staff. [p.15]

See also: Open Label

Cauda Equina Syndrome: a progressive neurologic syndrome characterized by lumbar pain, fecal and urinary incontinence, and possible progressive neurological deficits caused by soft and hard tissue proliferation often associated with lumbosacral vertebral or disc damage (also see Conus Medullaris). [p.11]

Central Nervous System (CNS): The brain and spinal cord. Information coming to the CNS or leaving the CNS is conducted along nerves of the Peripheral Nervous System (or PNS). [p.19]

Clinical Endpoint: a specified or targeted outcome of a clinical trial, which is based on an evaluation of the feeling, function or survival of a patient (subject). The results of a clinical trial generally evaluate the statistically valid difference between the number of people enrolled in the experimental treatment group who reached the pre-determined clinical endpoint as compared to the number of people who achieved the same clinical endpoint from the control group. [p.14]

Clinical Trial: a research study in human subjects to determine the efficacy of a new therapy or drug. See Section 4. [p.10]

Complete and Incomplete SCI: terms used to describe the overall severity of SCI. Technically, SCI is classified as complete if there is no motor or sensory function preservation in the sacral (most caudal) spinal segments. Thus, incomplete SCI is where there is some preserved motor or sensory function at the lowest sacral spinal level (S4/5). There can be extensive variability in the degree of preserved function after incomplete SCI. [p.12]

Conus Medullaris: the conus medullaris is the terminal end of the spinal cord. It occurs near the first lumbar vertebrae (L1). After the spinal cord terminates, the lumbar and sacral spinal nerves continue as dangling spinal nerves within the vertebral canal called the cauda equina. [p.11]

Control: the comparison group in a clinical trial, which does not receive the experimental treatment being investigated. The control group may receive a placebo, another treatment, or no treatment other than the current available standard of treatment and care for SCI. The outcomes of the experimental treatment group of subjects are compared to the outcomes of the control group. The use of a control group enables researchers to statistically determine whether the new experimental treatment provides a clinical (functional) benefit for the treatment of SCI. [p.14]

Dermatome: an area of skin innervated by sensory fibers which travel along a single spinal nerve that enters the spinal cord at a known level (or segment) of the spinal cord. Dermatomal Maps have been constructed for the human body (see Figure 2) to evaluate the preservation of sensation throughout different parts of the body. [p.35]

Diagnosis: a label encompassing a cluster of signs and symptoms, syndromes, or categories. It is also the decision reached as a result of the diagnostic process, which is the evaluation of information obtained from the patient examination organized into clusters, syndromes, or categories. [p.23]

Disk: see Herniated Disk

Dislocation: a disturbance or disarrangement of the usual relationship of vertebral bones of the spinal column.

Distraction: the act of pulling apart the overlapping vertebral segments.

Edema: an accumulation of fluid, often occurring as part of the inflammatory process after trauma. [p.23]

Electrophysiological Testing: the process of examining the relationships of body functions to electrical phenomena, such as the effects of electrical stimulation of peripheral nerves or the CNS, the production of electrical currents by organs and tissues, and the therapeutic use of electrical current. [p.22]

EMG (or Electromyography): the recording of the electrical signals associated with the activity (e.g. contraction) of a muscle. [p.23]

Evoked Potentials: the electrical signals recorded in response to the non-painful electrical or magnetic stimulation of the brain (via surface electrodes on the scalp) or a peripheral nerve. For example, a Somatosensory Evoked Potential (SEP or SSEP) is the signal recorded from the surface of the scalp overlying the sensory cortex of the brain in response to stimulation of a peripheral nerve (e.g. a leg nerve) and tests the functional activity of CNS pathways conducting sensory stimuli. A Motor Evoked Potential (MEP) is the signal recorded from a peripheral nerve or muscle in response to non-painful electrical or magnetic

stimulation of the motor cortex (via the surface of the scalp) and tests the functional activity of CNS pathways conducting motor (movement) commands. [p.23]

Functional Electrical Stimulation (FES): treatment through the application of electricity to the peripheral nerves that arise from the spinal cord. One application would be FES to particular peripheral nerves to allow a weak or paralyzed muscle to make a functional and purposeful movement (e.g. phrenic nerve FES for breathing). [p.26]

Functional Independence Measure (FIM): records the severity of disability of people after a disabling disorder. The 18 FIM items define two statistically and clinically different indicators. Thirteen items define disability in motor functions. Five items define disability in cognitive functions. FIM was not specifically designed for any single disability situation such as spinal injury. [p.22]

Functional Recovery: an improved change in the ability to perform a physical action, activity, or task in a typically expected or useful manner. [p.26]

Gait: the manner in which a person walks, characterized by rhythm, cadence, step, stride, and speed.

Glia: usually non-impulse conducting cells of the CNS. Glial cells function primarily as physical support for neurons. Others regulate the internal environment of the brain, especially the fluid surrounding neurons and their synapses, and provide nutrition to nerve cells. Glia have important developmental roles, guiding migration of neurons in early development, and producing molecules that modify the growth of axons and dendrites. These same functions may be important to repair after spinal cord or brain injury. There are 3 main types of glia within the CNS: astrocytes, microglia, and oligodendrocytes. Astrocytes can become inflamed (reactive) after spinal injury, which may be protective by limiting further damage, but this reactive astrogliosis may also block repair. Within the CNS, microglia have similar functions to macrophages within the bloodstream; they protect the brain and spinal cord from foreign substances and cells and remove dead or dying cells from the CNS. Oligodendrocytes form the myelin sheaths that surround (cover) axons. Myelin speeds the conduction of impulses along an axon, but it may also restrict spontaneous growth of axons during adult life (generally a good idea). After a spinal injury, the presence of myelin may interfere with functional repair. Myelin surrounding the axons of peripheral motor or sensory axons is formed by Schwann cells which do not inhibit axonal repair after injury. [p.25]

Good Manufacturing Practices (GMP): set of regulations, codes, and guidelines for the manufacture of drug substances (also known as active pharmaceutical ingredients, or APIs) and drug products (known as medicinal products in Europe), medical devices, in vivo and in vitro diagnostic products, and foods. In the United States GMPs are referred to as "cGMPs" or "current Good Manufacturing Practices" GMP is a term that is recognized worldwide for the control and management of manufacturing and quality control testing of pharmaceutical products. [p.17]

Helsinki Declaration: the Helsinki Declaration was developed by the World Medical Association and is a set of ethical principles for the medical community regarding human experimentation. It was originally adopted in June 1964 and has since been amended multiple times. The recommendations concerning the guidance of physicians involved in medical research may be found at www.wma.net/e/policy/b3.htm (also see Belmont Report) [p.18]

Herniated Disk: the protrusion of one of the spinal disks, between the vertebra, into an opening in the spinal cord, thereby compressing the incoming or outgoing nerve roots, which can cause numbness, pain, or muscle weakness.

ICH: the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH brings together the regulatory authorities of Europe, Japan and North America with experts from the pharmaceutical industry to discuss scientific and technical aspects of product registration. The purpose is to make recommendations on ways to achieve greater harmonization in the interpretation and application of technical guidelines and requirements for pharmaceutical product registration. The objective of such harmonization is a more economical and ethical use of human, animal and material resources, and the elimination of unnecessary delay in the global development and availability of new medicines whilst maintaining safeguards on quality, safety and efficacy, and regulatory obligations to protect public health. www.ich.org. [p.19]

Incomplete SCI: see Complete and Incomplete SCI [p.12]

Kinematic: having to do with the possible motions of a part or all of the human body. Kinematic analysis of movement is a highly technical evaluation, which may become easier and faster to accomplish with advances in computer generated images (CGI).

Microglia: see Glia. [p.25]

Microvolt, Millivolt: a microvolt is one millionth of a volt; a millivolt is one thousandth of a volt.

Motor-evoked potentials: see Evoked potentials [p.23]

Myelin: See Glia. [p.25]

Neurological Level of Spinal Injury: generally the lowest segment of the spinal cord with normal sensory and motor function on both sides of the body. However, the spinal level at which normal function is found often differs on each side of the body, as well as in terms of preserved sensory and motor function. Thus, up to four different segments may be identified in determining the neurological level and each of these segments is recorded separately and a single level descriptor is not used. Note: the level of spinal column injury may not correlate with the neurological level of spinal cord injury. [p11]

Neuron: any of the impulse-conducting cells that constitute the brain, spinal cord, and peripheral nerves (also called nerve cell). Sensory neurons relay information from sense organs (e.g. within skin and muscle) to the CNS, motor neurons carry impulses from the CNS to muscles and glands, and interneurons transmit impulses between sensory and motor neurons within the CNS (brain and spinal cord). A typical neuron consists of dendrites (fibers that receive stimuli and conduct them inward), a cell body (a nucleated body that receives input from dendrites), and an axon (a fiber that conducts the nerve impulse from the cell body outward to the axon terminals). Both axons and dendrites may be referred to as nerve fibers. Impulses are relayed by neurotransmitter chemicals released by the axon terminals across the synapses (junctions between neurons or between a neuron and an effector cell, such as a muscle cell). Large axons are insulated by a myelin sheath formed by glial cells (see Glia). [p.25]

Neuropathic Pain: usually perceived as a steady burning and/or "pins and needles" and/or "electric shock" sensations. The difference is due to the fact that "ordinary" pain stimulates only pain nerves, while neuropathic pain is often the result of impulses from both pain and non-pain (touch, warm, cool) sensory nerves within the same area, producing signals that the spinal cord and brain do not normally expect to receive. After SCI, neuropathic pain can occur "above level" in a region of preserved sensation above the level of SCI, "at level" located at the level of SCI and may originate within a nerve root or the spinal cord, or "below level" also known as central pain as this definitely originates within the spinal cord or brain. A characteristic of neuropathic pain is the perception of pain in response to a normal, innocuous stimulus such as a light touch; this is called allodynia. [p.30]

Nutraceutical: non-drug substances that are produced in a purified or extracted form and are administered orally to provide compounds the intent of improving health and well-being. These substances are not always controlled or approved by

government health regulatory agency prior to or after sale. A nutraceutical may be a specific component of a food, such as the Omega-3 fish oil that can be derived from salmon and other cold-water fish.

Oedema: See Edema

Oligodendrocyte: See Glia. [p.25]

Open label: both the researcher and the trial participant know the treatment that the participant is receiving. See also: Blinded assessments. [p.14]

Pain: See Neuropathic Pain [p.30]

Paraplegia: the term used to refer to functional loss below the level of the upper extremities, which may involve loss of motor and/or sensory function within the trunk, and/or the lower extremities. This implies damage to the spinal cord below the level of C8 and may include damage to conus medullaris or cauda equina (i.e. neural tissue within the spinal canal). [p.10]

Peer-reviewed: a scholarly work such as a manuscript or grant application that is read and assessed by other experts in the same field, to ensure that the author has met scientific standards. [p.10]

Pharmacodynamics: the study of the biochemical and physiological effects of drugs and the mechanisms of drug action and the relationship between drug concentration and effect. [p.13]

Pharmacokinetics: the study of the fate of drugs in the body, with emphasis on the time required for absorption, distribution within body tissues, the mode and extent of metabolism, or breakdown and the method of excretion. [p.13]

Preclinical: the term used to describe scientific experiments conducted prior to a human clinical trial and may include *in vivo* studies of animal models of the disorder (e.g. SCI) or examination of appropriate target cells in an in vitro culture situation. [p.10]

Placebo: An inactive substance or treatment that has the same appearance as the experimental treatment, but does not confer a physiological (functional) benefit for the disorder being investigated. A *placebo effect* is a physical or emotional change, occurring after an experimental treatment is taken or administered that is not the result of any physiological action of the treatment. The change may be beneficial in the short term and more accurately reflects the expectations of the participant and/or the expectations of the investigator providing the treatment (also see bias). A placebo drug or sham surgery can help distinguish the psychological effects of the experimental treatment from any physiological effects. [p.14]

Plasticity: refers to the changes that occur in the organization of the CNS; for example, the changes that occur after CNS damage to the structure and connections of neurons and glia (i.e. neural circuits) or to the CNS regions controlling specific functions, as a result of the effect of learning and training. A common and surprising consequence of CNS plasticity is that the location of a given function can "move" from one location to another in the brain due to repeated training after traumatic injury. The concept of plasticity can be applied to molecular and functional events. The phenomenon itself is complex and involves many levels of organization, including the expression of adaptive or alternative strategies via the appearance of newly developed neural circuits. The main thing is the adult CNS is not "hard-wired" with fixed and immutable neural connections. We simply do not know all of the conditions that can enhance neural plasticity in the intact or damaged brain and spinal cord. There is evidence that neurogenesis, the formation of new nerve cells, occurs in the adult human brain and spinal cord and such changes can also persist well into old age. [p.29]

Prosepective: In terms of a clinical trial, it means to study the effects of an experimental treatment on a "go-forward" basis, which is the opposite of a retrospective study which looks back historically on the outcomes of a patient group. A prospective study is where the methods of data collection and analysis are specified in a protocol before the study is begun (prospective). Patients are subsequently recruited and randomly assigned to receive either the experimental or control treatment and the outcomes are collected prospectively (in a go-forward manner). Also see: control subjects, placebo, RCT. [p. 14]

Quadraplegia: see Tetraplegia

Range of Motion: describes the space, distance, or angle through which a person can move a joint or series of joints in their arms and legs. [p.26]

RCT: Randomized Control Trial: a clinical trial in which the subjects enrolled are randomly assigned to either the experimental treatment arm (group) or control (placebo) study arm of the trial. It is the preferred clinical trial protocol to be used in all pivotal clinical trial phases (e.g. Phase 3 trials). [p.14]

Schwann Cell: See Glia. [p.25]

SCIM: Spinal Cord Independence Measure. A scale for assessing function and activities of daily life that appears to be more sensitive and accurate for assessing SCI than the Functional Independence Measure (FIM). SCIM has now gone through a few iterations[40 41] and is undergoing further refinement in multi-national studies. The SCIM is a 100-point disability scale developed specifically for SCI with emphasis on 18 activities associated with:

1. Self-care (feeding, bathing, dressing, grooming) max. = 20 points
2. Respiration and sphincter management (breathing, bladder, bowel, use of toilet) max. = 40 points (clinically weighted)
3. Mobility (in bed, transfers, indoors and outdoors, wheelchair, walking) max. = 40 points. [p.22]

Sham operative procedure: a surgical procedure in which the subject is operated on but does not receive the experimental intervention. [p.15]

Somatosensory evoked potentials: see Evoked potentials [p.23]

Spasticity: involuntary increase in muscle tone (tension) that occurs following injury to the brain or spinal cord, causing the muscles to resist being moved. Characteristics may include increase in deep tendon reflexes, resistance to passive stretch, clasp knife phenomenon, and clonus (limb movements characterized by rapid alternating contractions and relaxations of muscles). Clonus is frequently observed after SCI when the individual also has spasticity. A more scientific definition of spasticity is a velocity-dependent, increased resistance to passive muscle stretch. In other words, when a spastic muscle is stretched, it is harder to move the muscle than normal, and the faster the muscle is stretched, the harder the muscle is to move. [p.19]

Surrogate endpoints: A measurement of a drug's biologic activity that substitutes for the clinical (functional) endpoint that may predict a patient's final clinical outcome. A surrogate marker (measure) may indicate whether a drug is effective without having to rely on the longer term functional clinical endpoints being achieved. The identification of an accurate surrogate measure or marker can reduce the time required in a clinical trial phase to show a possible benefit. Surrogate endpoints can and have been used in Phase 2 clinical trials. [p.22]]

Tetraplegia (also known as quadraplegia): the term used to refer to loss of motor and/or sensory function due to damage to the spinal cord, with impairment of the upper extremities as well as trunk, legs and pelvic organs. This implies damage to the spinal cord at or above the T1 level. [p.10]

Zone of Partial Preservation (ZPP): only used when SCI is complete and refers to those segments below the neurological level of injury where there is some preservation of impaired motor or sensory function (usually, but not always, within a few segments of the neurological level).

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International Spinal Research Trust: www.spinal-research.org

Fondation internationale pour la recherche en paraplégie: www.irp.ch

Japan Spinal Cord Foundation: www.jscf.org

Miami Project to Cure Paralysis: www.themiamiproject.org

Neil Sachse Foundation: www.nsf.org.au

Paralyzed Veterans of America: www.pva.org

Rick Hansen Foundation: www.rickhansen.com

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