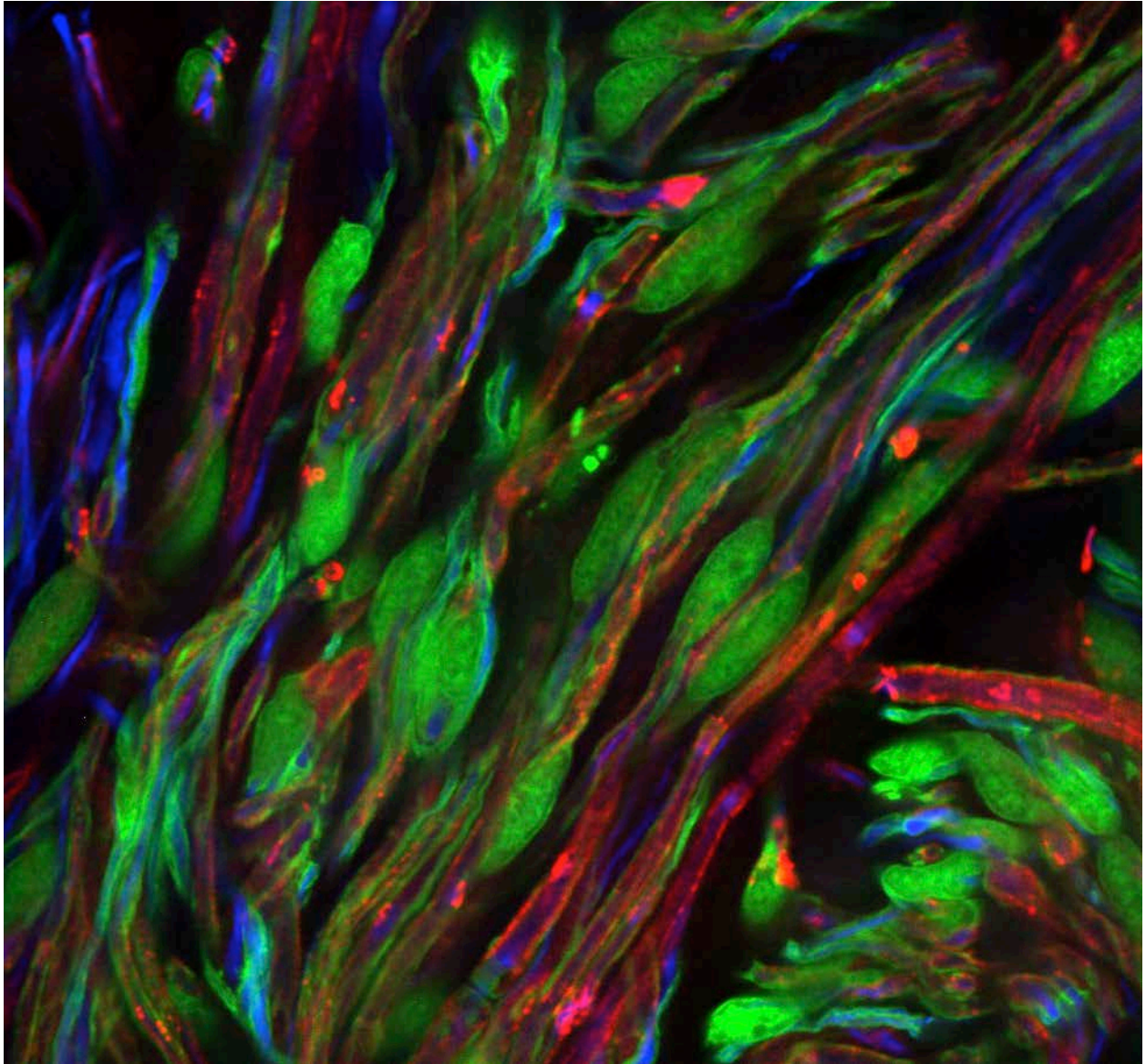


## Experimental treatments for spinal cord injury: What you should know (Version 2)



A guide for people living with spinal cord injury,  
their family, friends and health care professionals

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## Note:

**This guide can be freely printed or downloaded to any website (in an unaltered state).**

Unlocked versions are available for translation (contact Dr. John Steeves, see below).

**Disclaimer:** This guide is based on published scientific papers and the professional opinions of the authors as of 2012. The fundamental information is similar to version 1 (2006) of this document. The recommendations are subject to change as new knowledge becomes available. This document is intended to be an additional resource for you, and is not intended to substitute for the advice and direction of your health care provider, or replace current clinical treatments. Users of this guide should periodically review the material to ensure that the advice herein is consistent with protocols of any experimental treatment being offered to improve functional outcomes after spinal cord injury.

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## Experimental Treatments for Spinal Cord Injury: What you should know (Version 2)

Sustaining a spinal cord injury (**SCI**) is extremely traumatic, both physically and psychologically. You may have already had surgery to stabilize the spinal column and reduce the possibility of further damage. You are understandably distressed about the functions you may have lost below the level of spinal injury. You wish to recover any lost abilities as soon as possible. You, your family or friends may have searched the Internet for treatments and cures.

After a spinal cord injury, patients are often told that there are no validated drug or cell transplant treatments that will repair the damage and restore voluntary movement. Regardless of what you may hear or read, this is still true. This advice is given with the best intentions, in the hope that people will focus on their rehabilitation and recovery programs, rather than looking for a miracle cure. Nevertheless, great advances have been made in the science of spinal cord repair and treatments that could one day improve the function of people living with SCI are being tested in animals. But there are also people who might offer you an unproven treatment, claiming they can restore function if you have money to pay!

This document was first created in 2006 and has now been revised and updated as of 2012. It is intended to address some of the questions you may have concerning various therapies or treatments after SCI. You are

encouraged to discuss these issues with your health care team.

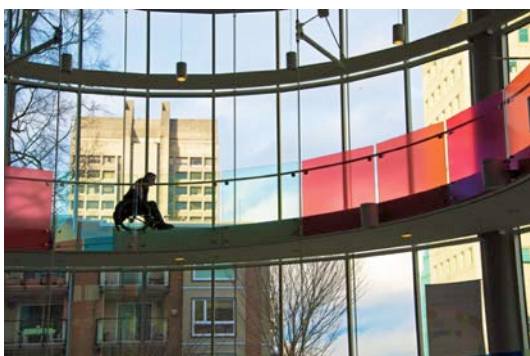


### ***How do I tell whether a treatment is part of a valid clinical trial program?***

It can be difficult to tell the difference between a bona fide clinical trial and a treatment program that claims to be a trial. Perhaps the easiest way to tell the difference is whether the investigator or clinic is asking you to pay for the treatment. If you, your family or friends are asked to pay for an experimental treatment, it is probably not a clinical trial! You should be cautious about any experimental treatment being offered for payment. This booklet offers advice to help you make an informed decision about participating in a trial, as well as to avoid paying for unproven experimental treatments and placing yourself at risk. There are 5 appendices (A-E) attached to this booklet.

In this booklet we also provide an update of past research approaches and where their progress stands at this time. Although validated restorative treatments of the spinal tissue have yet to be established, there are a number of clinical trials (as of 2012) currently underway or about to commence (please see **APPENDIX A** of this booklet).

You are curious, but hopefully cautious, and wish to know how to best evaluate the credibility of a new treatment or a clinical trial before agreeing to participate. You want to know what questions to ask and what answers you should expect from someone explaining a clinical trial or offering an experimental treatment (please see attached questionnaire - **APPENDIX B** at end of booklet). The differences between a rigorous clinical trial and any "experimental treatment" being offered for payment can be confusing.



### ***Why are clinical trials necessary?***

It can be surprisingly difficult to find out if a treatment or therapy is safe and if it really works. If a patient receives an experimental therapy and experiences some recovery, they commonly believe they got better as a direct result of the new treatment. But the improvement may not have been caused by the treatment. There are two other possibilities to consider.

*Rehabilitation Benefits and "Spontaneous" Recovery.* Immediately after a spinal cord injury, some people are completely paralyzed below the area of injury. However, spontaneously, or more often with active rehabilitation programs, most people will recover at least a little function, while some recover more function and a small number of

people will achieve dramatic recovery. The rehabilitation treatments people receive after SCI (e.g. strength training exercises, therapies to improve mobility and/or hand function) will provide improvement in activities of daily living and mobility. The rate of recovery is usually greatest over the first three months, but with continued rehabilitation effort, functional improvement can continue for a year or even more.

There is wide spread consensus that rehabilitation training maximizes greater independence for activities of daily living and improves mobility. Physical and occupational rehabilitation training is now widely available. Even the controversial "medical tourism" clinics, offering cell transplants to people, include vigorous rehabilitation. Thus, for people who have received an experimental drug or cell transplant, it can be difficult to tell whether recovery is due to some unrecognized spontaneous healing, the effects of rehabilitation, or the effect of the experimental treatment. Effective clinical trials are designed to accurately and reliably determine which of these possibilities is the cause of any observed recovery.

*The Placebo Effect.* Everyone has hopes and aspirations, including scientists, clinicians and patients. In medicine, our desires can lead us to expect or report outcomes that are not the result of a therapy. Thus, even after receiving a control substance, containing no medication, a patient's hope may influence their perception and lead them to report an improvement. Likewise, the unintended biases of scientists and clinical investigators can lead them to conclude a therapy has benefit when the improvement is due to some other influence.

To truly understand whether there is a causal relationship between a therapeutic intervention and any subsequent improvement, we need to compare outcomes of a group of patients who received the treatment to those in a control group who did not. While not always feasible, a placebo or "sham" treatment given to a group of control subjects (without letting either the patients or the clinicians know who is receiving the active treatment or the placebo control) is the most effective way to accurately measure whether there are beneficial effects of the therapy. In fact, without some type of control group during the later stages (Phase 2 or 3) of a clinical trial program, the research study will not be able to provide valid evidence of the therapeutic effects - good or bad. In a trial, randomly selected control patients will receive a sham or placebo treatment and they will sometimes also report a considerable improvement in their condition. If the improvement in the control subjects is just as large as that reported by subjects receiving the actual experimental treatment, it is only logical and reasonable to conclude the experimental treatment has little or no therapeutic benefit.

***If an experimental therapeutic has not completed a properly designed clinical trial program, there is a real danger that treatments that do not work or therapies that might do harm could become standard medical care.***

### **What makes a good clinical trial?**

People with spinal injuries want to recover as soon as possible. Scientists also want to see their discoveries help people with spinal injuries. Physicians, surgeons and

therapists want the treatments they provide to improve an individual's independence, mobility and quality of life. If human studies are not adequately controlled, the desire (unintended biases) of people living with SCI or those of scientists and clinical investigators may lead them to conclude an improved function. This is why it is best to "blind" both the trial participants and the investigators as to which person received what treatment (experimental or placebo control). Sometimes this cannot always be accomplished, but the investigator charged with measuring any improved function (outcome) must be "blinded" (kept from knowing) what treatment was administered to the trial participant being examined.

Bias on the part of doctors ("investigators") who conduct clinical trials can pose a significant risk for the misinterpretation of trial data or, even worse, can lead to short-cuts in the scientific process of a trial, resulting in harm to people. Sometimes this bias is unintentional. While clinical trial investigators may be reimbursed for their work in conducting the research, they should not have a direct financial interest in the outcome of the trial (such as owning stock or other equity share in the sponsoring company). If an investigator could benefit financially from the outcomes of a human study,, there is the possible temptation to report a positive benefit. Institutional Review Boards (the independent panels that safeguard patient rights and must approve scientific clinical trials) have strict standards for investigator disclosure of potential financial conflicts of interest. Patients should be made aware of any potential conflicts of interest situation by the investigators as a part of the informed consent process.

If this is not disclosed, then it is within your rights to ask.

A good (valid) clinical trial (human study) usually will test a treatment only after it has undergone extensive investigation in animals, or in some other related human disorder, and will have shown evidence of safety and a potential for a beneficial effect. A clinical trial program has several phases (see below). It will be carefully designed to compare a group of participants receiving the experimental treatment with others (controls) receiving no treatment (or sham procedure), a placebo substance or the current best standard of care. Without completing a clinical trial that compares the effects of a treatment in the experimental group to the outcomes from an appropriate control group, it is impossible to determine if the treatment is safe and provides a meaningful benefit.

*Treatments offered for material gain:* Unfortunately, if patients are desperate, as they might be after SCI, there is an opportunity for less scrupulous organizations to offer unproven treatments to those who can pay. You should question any request for payment of an “experimental” clinical trial procedure, as this is not allowed in valid clinical trial programs. Depending on your health care coverage, you, your health care or government insurance plan may be expected to pay for the current standard of medical care you receive during your participation in a clinical trial. You should ask and discuss what, if any, payment is required for your participation in a trial, but the treatment itself and all the following assessments should be free.

Creating new treatments for those with spinal or brain injuries is one

of the most difficult challenges medicine has ever attempted. Yes, like winning the grand prize in a large lottery, there is a very small chance that a treatment offered without completing a clinical trial might work, but it is much more likely that it will be ineffective or even do harm. We strongly advise you to only participate in objective clinical trials where there is compelling evidence of positive benefits from previous animal experiments or use of the treatment in a related clinical disorder.



### **What if I have already participated in a previous clinical trial?**

The following might not apply to most people currently living with SCI. Nevertheless, patients who have already participated in a previous clinical trial, such as an experimental therapy for SCI (sanctioned by regulatory authorities or not), may or may not be eligible to participate in a subsequent trial. The reason for this is that a previous therapy may have altered the spinal cord in subtle unknown ways, making it difficult to know whether the current treatment has a benefit. You must discuss with the investigators of the current trial, any of your past experiences with experimental therapies. Nevertheless, should a treatment be subsequently approved as

a treatment for SCI, you may be able to receive that treatment, providing you meet the eligibility requirements (for example, the treatment benefits a person who has lived for some time with SCI).

### **How are clinical trials structured and governed?**

The key component of most clinical trials is the random assignment of participants to either an experimental treatment group or control group. As mentioned above, the control group helps eliminate the possibility that many other factors, which cannot be controlled by the design of the study, could influence the trial outcomes. Random assignment helps ensure that these other factors influence the groups equally. For example, most people receive active rehabilitation after SCI. By itself, rehabilitation can improve function in people living with SCI, which is why we recommend you participate in available rehabilitation opportunities. Thus without a control group that will receive a similar amount of active rehabilitation, the investigators would not know whether any observed improvement was specifically due to the experimental treatment being tested.

An exception to the use of a separate control group may be made in a trial where patients have established a very stable level of function (this would normally be people who have lived with SCI for at least 6-12 months). In this event, the participants may act as their own control and their capabilities will be measured before and after a treatment to see if there is an improvement. Sometimes two groups are used with one group receiving the experimental treatment followed by a period with the

placebo control, while the other group receives the placebo control first, followed by the experimental treatment. Regardless, the examiners assessing the outcomes in such trials are "blinded" as to what was done and at what time.

Another exception relates to early Phase 1 clinical trials (see below), which primarily focus on testing the safety and the feasibility for offering the treatment. These early studies are usually accomplished with a small number of participants and are generally completed without a control group. Nevertheless, a control group will be part of any subsequent Phase 2 or Phase 3 trials that test whether the treatment is effective.

As mentioned above, it is also important to eliminate bias by trial investigators or study subjects. This is why trial programs that successfully pass Phase 1 safety evaluation always have a later trials to examine efficacy where the investigators are "blinded" to which group a subject belongs (experimental or control). Whenever possible, neither the subjects receiving the experimental treatment or the placebo, nor the doctors or therapists assessing the subjects know who received what treatment. Such a "blinded" protocol preserves the objectivity that is necessary to accurately determine whether a treatment is safe and beneficial.

Finally, valid clinical trials should be registered with the appropriate national regulatory authority (such as the Food and Drug Administration, FDA, in the United States or the European Medicines Agency, EMA). Bona fide trials will have approval from the local human research ethics committee (such as an Institutional Review Board or



IRB). An increasingly common occurrence is the registration of the trial on a central website.

(<http://www.clinicaltrials.gov>)



The ClinicalTrials.Gov website can serve as a source of valuable information for patients, clinicians and scientists. The physician investigator asking you whether you wish to participate in a clinical trial will provide you documented evidence that all national and local regulatory and ethical human study approvals have been obtained.

### **What is required for your participation in a clinical trial?**

Before anyone can be enrolled in a trial they are usually screened against a set of pre-determined criteria to see if they qualify to participate in the proposed clinical study. Not all patients will qualify to participate in a given trial. Every trial should have specific conditions (inclusion / exclusion criteria) that must be satisfied for an individual to participate. Most experimental treatments have a history of being better for certain conditions and situations. For example, the past evidence may indicate a drug or cell transplant should be administered within a specific time window after SCI and your injury may now be outside that

timeframe. The location and severity of your spinal cord injury may or may not meet the eligibility requirements, or you may have other conditions that would limit your suitability for participation or for proper evaluation.

When an experimental treatment is being examined in a clinical trial, it is usually important that all the participants be fairly similar to each other (in terms of their symptoms). Too much variability between subjects can confuse and alter the accurate determination of the trial results. Like many neurological disorders, SCI can result in varying degrees of impairments and you have probably already noted that you have been initially classified along a scale extending from complete sensory and motor loss to very minimal sensory or motor loss. If we were to put all the different types of SCI subjects into one group, it is likely that the different degrees of spontaneous recovery would make it difficult to determine whether the experimental therapy was beneficial. This is why clinical trial programs are often repeated for each sub-type of a disorder or disease.

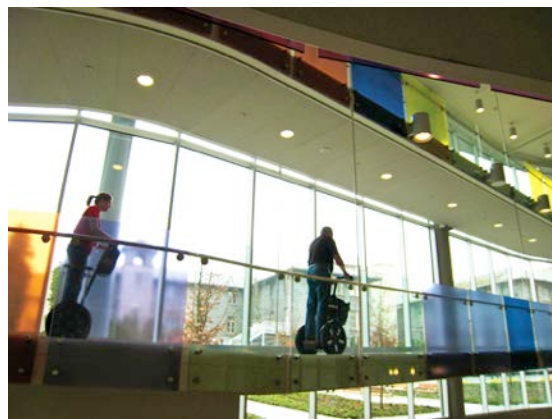
### ***What is informed consent?***

Should you meet the eligibility requirements to participate in a clinical trial, you must also give informed consent. This involves a discussion with a trial investigator about the specific trial where:

1. You should have the nature of the experimental therapy explained to you in detail, including prior evidence in animal studies or other clinical disorders;
2. You should be told about the potential benefits and risks of participating in the trial;

3. You should be told that you may be randomly assigned to either the experimental treatment group or the placebo control group (or why the trial at this phase does not include a control group);
4. You should be informed of all study procedures, the duration of your participation, and what is required of you for follow-up visits;
5. You should understand how the cost of any standard clinical care or rehabilitation training, accompanying or associated with the trial (including travel costs), will be covered;
6. You should be told if you will receive compensation to participate in the trial
7. You should be told how treatment or compensation for possible research-related injury will be arranged and who will pay for it;
8. You should be informed of the alternatives to participation in the clinical trial;
9. You should be informed of your right to withdraw from participation in the study at any time for any reason; you should also be informed that the investigators may remove you from the study and the possible reasons;
10. You should have adequate time to ask questions and be fully satisfied that your questions have been answered.

One way to judge the quality of a clinical trial is the thoroughness of the informed consent and the care that is taken to fully inform you about all significant risks. This is especially important when the long-term effects of a treatment are not well understood.



### ***How long will I be required to participate in the clinical trial?***

After the informed consent process is complete and you have formally volunteered (enrolled) as a participant, you are likely to be randomly assigned to either the experimental treatment group or control group. You may or may not know whether you will receive the experimental treatment or the control treatment; remember, "blinding" is important to objective results. You will then undergo an initial baseline assessment to confirm your status and describe your capabilities at the beginning of the trial. During the trial, there will be some follow up assessments where it will be necessary to attend the clinic. Clinical trials may last for different periods of time, depending on the type of treatment involved, but follow-up examinations may be required at intervals for several months or even a few years. These details should be explained to you at the time you are explained informed consent.

In some trials you will be asked to donate several hours so that thorough assessments can be performed. Most of these examinations involve little or no discomfort and may include a physical exam, routine blood tests, and assessment for the capacity to perform activities of daily living. Imaging studies

such as MRI may be obtained and tests of spinal cord conduction may require electrodes to be placed on your skin so electrical activity can be measured across the injury. These evaluations are used to examine what changes, if any, have occurred in spinal cord function. You should not have to pay for these visits, but travel and accommodation expenses should be paid.

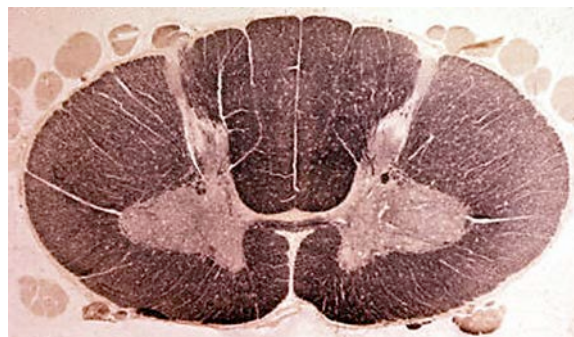
It usually takes a progression through three separate clinical trial phases before an experimental treatment will be approved by a government regulatory agency for use in humans with that specific disorder. Each trial phase is more demanding than the previous phase in terms of how it is conducted. You would likely only be involved in one trial phase, and you should be told where the testing stands and in which phase of the trial program you are participating.

### What are the various trial phases?

**Phase 1** is to find out if the treatment is safe and possible to adequately test in human subjects. A fairly small number of participants, usually less than 50, are given the treatment (often at slightly different doses) to see if there are any unexpected, harmful side effects. This is the one clinical trial phase where there might not be any control subjects, as the emphasis is on safety and tolerability of the experimental treatment. Phase 1 trials are sometimes referred to as "open label" trials as everyone (participants and investigators) knows the treatment and there are no "blinded" assessments. A series of routine clinical tests are undertaken and the participant is asked to report any discomfort or change in body function. Sometimes,

functional activity assessments are also included as part of the Phase 1 study, but conclusions will not be made about the benefit of the treatment. It should be noted that safety is always monitored throughout all clinical trial phases.

**Phase 2** is a second round of studies designed to assess whether the treatment stimulates any positive biological activity within the target tissue or provides a clinically meaningful benefit for the intended body functions. The outcomes from the experimental group are compared to the control group receiving an appropriate placebo treatment or standard of care. Because Phase 2 trials often involve as many as 200 experimental and control subjects, they frequently include multiple study centers. Phase 2 trials are commonly used to determine the best dose and timing of treatment, as well as the best outcome tools to measure any positive (or negative) effects of a treatment. This development phase is important to establishing the best protocol for the pivotal Phase 3 study. Even if the evidence from Phase 2 studies suggests a possible benefit, this still does not usually prove that the treatment will be reliably effective as the number of participants is still relatively small. Generally, the therapeutic must complete the most important (pivotal) stage - Phase 3.



**Phase 3** is the pivotal trial phase to more fully test the effectiveness and safety of the therapy and involves the largest number of participants at multiple locations (often in several countries). This phase helps the investigators learn if the treatment works well enough to improve outcomes in a more varied population, typically men and women, different ages, races, etc. Furthermore, it helps ensure that different centers can provide the treatment in the same manner and equally well. If the treatment demonstrates a clear benefit with no serious side effects (adverse events) then it is eligible for consideration for approval by a national regulatory agency as a treatment for the disorder being studied in the trial.

### **What if you get assigned to the control group?**

Most patients would obviously prefer to receive a beneficial treatment. However, when studying an experimental treatment in a clinical trial program, we do not know whether it has any benefits or significant risks. As we described above, it is impossible to learn if a treatment really works and is reasonably safe unless there are appropriate control patients with whom to make comparisons. If we already were certain that available evidence proved a treatment is effective, it would be unnecessary and unethical to delay treatment by further testing. By definition, for a trial to be valid, clinical investigators adopt a “wait and see” perspective about the risks and benefits, until all trial phases are completed. If by mischance the treatment has an undesirable or harmful side effect, then

being in the control group may be an advantage!

Volunteers participating in a trial, whether they are in the experimental or control group, should always receive the current best care available. The trial investigators will have a policy on what to offer members of the control group at the end of the trial, which may include the trial treatment if it is effective and you still meet the eligibility criteria. If this is not clear, you need to ask.

### **What should you expect after a SCI clinical trial?**

As of 2012, there are no approved cures for SCI. As you are already aware, the brain and spinal cord are the most complex tissues of the body and the most challenging to repair. We do know that some surgical procedures reduce the chance of further injury and active rehabilitation training programs can improve recovery or adaptive skills, especially when there is some preserved function below the level of spinal cord damage. If a new treatment is determined to provide some functional benefit after completing a clinical trial program, it is still unlikely that it will provide a complete cure.

Progress is incremental and it is most likely that a combination of treatments will provide better outcomes in the future. For example, cancer therapy often involves a combination of treatments, including surgery, drugs and radiation therapy. It took decades for scientists to determine the best combinations for current cancer therapy programs. With continued study, scientists and clinicians will also refine the most appropriate combinations for SCI.

## Where can you get good advice?

Reliable information is always the goal. You have a number of avenues you can explore. Whatever you choose to follow, you should confirm all information from more than one source. Some of your options are:

- You can discuss your options with your physician(s)
- You can visit several websites, which provide a variety of information. There are a number of professional societies, non-governmental spinal cord foundations, government agencies, and university or hospital-based research centers where you can seek advice. Many of them are staffed by people who themselves have spinal cord injuries.
- You can study the available published scientific and clinical literature. This may seem obvious, but it can also be intimidating if you don't have a biomedical research background. Nevertheless, the most important question you ever learned in life was the question - WHY?
- **Keep reading and keep asking questions.** An earlier version of this handout had a more extensive discussion of the above topics (some might say too detailed a description). However it is still available at the ICORD website (<http://www.icord.org>)

## What treatments are available now?

Patients with SCI should undergo appropriate surgical procedures when they are medically fit to withstand the surgery 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. Many factors impact the timing of any surgery including transport to a hospital capable of performing the necessary surgery. Worldwide, there is a developing practice for early surgical decompression of the compressed or contused (bruised) spinal cord (preferably within 24 hours of injury). Many surgeons agree that fractures of the vertebral spinal column should be stabilized, which may involve 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. During this procedure all abnormal pressure on the spinal cord and spinal nerves from should be reduced, maximizing the potential for recovery. For more details, on these and other treatments, please see <http://www.elearnsoci.org>



### What about Rehabilitation Strategies and Assistive Devices?

Many spinal cord injuries are incomplete and sometimes slightly 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 active rehabilitation 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.

Thus, there is an emerging consensus that *active* rehabilitation after SCI is important and effective in preserving body functions, as well as improving the recovery of functional activity 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 likely to be a part of any treatment protocol, but is unlikely to be

sufficient to maximize functional outcomes after SCI.

However, the consensus is any active rehabilitation is better than no rehabilitation. Once again, if an individual is medically stable and will not suffer any detrimental effects due to the movements associated with rehabilitation activities, then rehabilitation training can be started within weeks after SCI. There are an extensive number of activity dependent rehabilitation studies and trials underway. We cannot begin to cover these rehabilitation strategies. For a detailed discussion of the strength and limitation of the many rehabilitation strategies, please consult ([www.scireproject.com/](http://www.scireproject.com/)). Do not hesitate to discuss active rehabilitation strategies with your therapist and/or physician.



Active rehabilitation (physical, occupational, or psychosocial) is likely to magnify the benefits from any other therapeutic intervention for improving outcomes after SCI, including any drug or cell transplant. In addition, active rehabilitation maintains bone and muscle

integrity, fitness, and reduces ongoing medical complications 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 ([www.scireproject.com/](http://www.scireproject.com/)).

A number of currently available drug treatments can reduce spasticity and pain, or improve metabolic functions, as well as provide better management of bladder, bowel, respiration and cardiovascular activity. There are also programs to help people living with SCI have children. Engineers have developed a number of assistive devices to provide improved motor function and increase mobility within the community. Although these issues are of equal or greater importance to the quality of life for people living with SCI, it is beyond the scope of this article to cover the ongoing care and treatment of all medical challenges and community participation after SCI. Your health care professionals can advise and guide you.



### **What are some of the current experimental treatments proposed for SCI?**

With all that has been discussed so far, what is the current state of

experimental treatments for SCI? The accompanying table (**APPENDIX A**) lists some of the treatments that have been investigated and are currently being investigated in notable clinical trials. Potential therapeutic interventions (new drugs, cell transplants, rehabilitation strategies or assistive devices) are directed to one or more of several target categories:

- Neuroprotection - limiting the amount of tissue damage and rescuing injured nerve cells (neurons) to keep them from dying in the hours or possibly days following the injury
- Repair / Regeneration - reducing long-term pathology of the injured cord, promoting new outgrowth and connections from spinal neurons, possibly replacing lost cells to rebuild the damaged spinal cord
- Neuroplasticity - facilitating the formation of new functional connections between surviving cells and/or replacement cells, thereby enabling recovery of function through the creation of new circuits
- Replace / Assist function - incorporation of an assistive (engineered) device to improve independent activity and/or mobility

Researchers around the world are working hard to develop new treatments to achieve the above aims. Some treatments are showing promise in animal experiments; a few are already in early stage clinical trials ([see APPENDIX A below](#)).

## APPENDIX A: Previous Drug and Cell Transplant Clinical Trials and Studies

Treatment	Suggested Mechanism	Timing of Treatment & Status of Clinical Trial	Results Summary
Methylprednisolone sodium succinate (MPSS)	Anti-inflammatory corticosteroid; Neuroprotection	Acute SCI (< 8 hrs); completed several Phase 3 trials	Missed statistical significance on primary outcome (but still used in some centers). Undergoing combination trials (see below)
GM-1 (Sygen)	Ganglioside Neuroprotection and neural repair	Acute SCI; completed Phase 3 trial	Missed statistical significance on primary outcome (abandoned)
Thyrotropin-releasing hormone (TRH)	Neuroprotection	Acute SCI; completed Phase 2 trial	No significant benefit (abandoned)
Activated macrophage transplantation (Procord)	Neuroprotection and neural repair	Acute SCI; completed Phase 2;	No significant benefit (abandoned)
Fampridine (Dalfampridine, Ampyra, Fampyra)	blocks voltage sensitive potassium channels, prolongs action potential	Chronic SCI; completed Phase 3 trial	Missed statistical significance on primary outcome (but subsequently approved to improve walking in people living with multiple sclerosis)
Gacyclidine (GK-11)	Neuroprotection (glutamate NMDA channel antagonist)	Acute SCI; completed Phase 2 trial	Missed statistical significance (abandoned)
Cethrin (Rho antagonist)	intracellular cell signaling for axonal growth	Acute SCI; completed Phase 1/2 trial	Open-label (unblinded) results suggest possible benefit, but Phase 2 randomized control trial required
Minocycline (Minocin)	Anti-inflammatory (commonly used for acne)	Acute SCI completed Phase 2 trial with some statistical significance	Statistical significance achieved on some measures, but funding needed for Phase 3 trial program
Riluzole	Neuroprotection and neural repair	Acute SCI; completed Phase 1	Phase 1 trial completed, but no results published to date
Erythropoietin (EPO) - contraindicated when administered with MPSS	Anti-inflammatory also increases number of red blood cells	Acute SCI; Trial ongoing (but not registered with clinicaltrials.gov)	No trial results reported to date, (conflicting results reported in preclinical studies)
ATI-355 (anti-NOGO) antibody	Neuroprotection and neural repair	Acute SCI; completed Phase 1	No trial results reported to date,
Nasal mucosa transplantation (source of olfactory ensheathing cells)	Neuroprotection and neural repair	Chronic SCI, several open-label studies completed and one blinded Phase 1 study (Australia)	Several small studies report conflicting results about whether there are benefits after SCI.
Mesenchymal stem cell transplants	Neuroprotection and neural repair	Acute-Chronic SCI, studies ongoing (not registered with clinicaltrials.gov)	Several small studies report conflicting results about whether there are benefits after SCI.

Interventional clinical trials are routinely registered on [www.clinicaltrials.gov](http://www.clinicaltrials.gov) based on legal requirements\* and because scientific journals may require registration for publication of trial results. Investigators may choose not to register some early phase trials and those testing behavioral interventions are sometimes not registered, even though they may be important and scientifically rigorous studies.



## APPENDIX A: Current Drug and Cell Transplant Clinical Trials

<u>Sponsor / NCT</u>	<u>Intervention</u>	<u>Inclusion/ Exclusion/ Criteria</u>	<u>Treatment Timing &amp; Follow-up</u>	<u>Enroll</u>	<u>Study Phase</u>	<u>Primary Outcome</u>	<u>Comments</u>
Asubio Pharma. NCT01502631	IV drug SUN13837 daily for 28d. vs. placebo	18-80yr C4-C7 AIS A	Acute SCI SCI≤12hr 26wk F/U	Began 1/2012 USA/ Canada 164 subjects	Phase 2 RCT (Double Blind Placebo Control)	Efficacy/Safety ISNCSCI examination	Responder Definition: 2 Motor Level Improvement
Stem Cells, Inc NCT01321333	Direct surgical implant of neural stem cells into spinal cord	18-60yr Thoracic AIS A; then AIS B, C	Chronic SCI (>6 weeks post injury); 1-4 yr F/U	Began 4/2011 Zurich 12 subjects	Phase 1/2 Open Label	Safety and Tolerability/ Exploratory Efficacy	Cells from human stem cell line (allograft)
Totipotent RX Cell Therapy Pvt. Ltd. NCT01490242	IT infusion of Autologous Bone Marrow	18-60yr AIS A,B,C Below C4 level	Chronic SCI 6m-8yr 18 m F/U	Began 10/2011 India 15 subjects	Phase1/2 Single Group Open Label	Safety/Efficacy ISNCSCI motor sensory examination SCIM III	
Hospital Nacional de Paraplejicos de Toledo (Spain) NCT01329757	Daily SQ human Growth Hormone vs placebo dosing for 1 yr; 6 months of rehab	18-75yr C4-T12 AIS B, C	Chronic incomplete SCI >18m SCI 1 yr F/U	Began 4/2011 Spain 76 subjects	Phase 3 RCT (Placebo Control)	Efficacy/Safety ISNCSCI motor sensory examination; SCIM	Test of 1yr of daily SQ Growth Hormone to improve neural outcome in chronic incomplete
Wroclaw Medical University, Poland NCT01231893	Surgical implant of autologous olfactory ensheathing cells into spinal cord; intense rehabilitation	16-65yr C5-L5 AIS A	Subacute/Chronic SCI (not specified)	Began 5/2008 Poland 10 subjects	Phase 1 Open Label	Safety/Efficacy Not Specified	Subjects must be undergoing continuous rehabilitation
Tokyo University NCT01485458	Early (<24h) vs. Delayed (>2wk) Decompress surgery for acute cervical SCI without bony injury	20-79yr C5 or below AIS C tetraplegia No bone injury; Pre-existing cervical canal stenosis	Acute / Subacute Admitted within 48 hours of SCI 1yr F/U	Began 12/2011 Japan 100 subjects	Phase 1/2 RCT Open Label	Safety/Efficacy ISNCSCI motor sensory examination; SCIM; walking ability	Test whether timing of cord decompress is associated with improved neurological outcome in SCI

## Current Clinical Trials (continued)

<u>Sponsor / NCT</u>	<u>Intervention</u>	<u>Inclusion/ Exclusion Criteria</u>	<u>Treatment Timing &amp; Follow-up</u>	<u>Enroll</u>	<u>Phase of Study</u>	<u>Primary Outcome</u>	<u>Comments</u>
Guangzhou General Hospital/Guangzhou Military Command NCT01446640	IV and IT autologous bone marrow derived stromal cell infusions	16-60yr Thoracic or Lumbar SCI AIS A, B	Subacute / Chronic 2wk<SCI< 1 yr	Began 10/2011 China 20 subjects	Phase 1/2 Open Label	Safety/Efficacy Frankel Scale ISNCSCI motor sensory exam EMG/Neurophysiology	Non-randomized Single Group
General Hospital of Chinese Armed Police Forces NCT01393977	IT infusion of Umbilical cord blood stem cells Rehab of limb function	20-50yr Traumatic SCI (not otherwise specified)	Rx timing not specified  1yr F/U	Began 1/2011 China 60 subjects	Phase 2 Open Label	EMG/Neurophysiology BAEP (brainstem) Evoked potentials	Non-randomized multiple group comparison
Nordic Life Science Pipeline Inc. NCT01484184	Oral dosing of SPINALON (buspirone + levodopa + cardidopa); vs. placebo	18-65yr C3-T12 SCI AIS A, B	Chronic SCI SCI≥3m F/U 4hr post administration	To begin 5/2012 Canada 51 subjects	Phase 1/2 RCT (Double Blinded Placebo Control)	Safety/Tolerability Vital Signs Rhythmic Leg EMG	Multiple arms testing SPINALON vs. combination of drugs vs. placebo
China SCI Net (Hong Kong) NCT01471613	Implant of Umbilical Cord Blood cells; Lithium; Methylprednisolone	18-65yr C5-T10 level; AIS A SCI≥12m; stable 6m.	Chronic SCI SCI≥12m; stable for 6 m. 48wk F/U	Began 9/2010 China 60 subjects	Phase 1/2 RCT (Placebo Control)	Efficacy/Safety ISNCSCI motor sensory examination; walking; functional assessment	One of a sequence of ongoing China SCI Net SCI trials
China SCI Net NCT01046786	Surgical Injection of Umbilical cord blood mononuclear cells; ± IV methylprednisolone; ± oral lithium	18-69yr C5-T10 AIS A	Chronic SCI SCI≥12m Stable neuro≥6m F/U 48wk	Began 1/2012 China 20 subjects	Phase 1/2 Open Label	Safety/Efficacy ISNCSCI examination SCIM WISCI walking index	Open Label Dose-escalating trial
North Florida / South Georgia Veterans Health System NCT01272011	Locomotor training ± Hypoxia treatment	≥18yr C5-T11 AIS C, D O <sub>2</sub> sat 95-99% walks ± assist	Chronic SCI SCI≥12m F/U 2wk	Began 5/2010 Florida, USA 41 subjects	Not specified; RCT; (Placebo Control)	Minute ventilation; Propulsion generated during stepping	Test of whether hypoxia (1/3 less O <sub>2</sub> than room air) will improve walking

## Current Clinical Trials (continued)

<u>Sponsor / NCT</u>	<u>Intervention</u>	<u>Inclusion/ Exclusion Criteria</u>	<u>Treatment Timing &amp; Follow-up</u>	<u>Enroll</u>	<u>Phase of Study</u>	<u>Primary Outcome</u>	<u>Comments</u>
Emory University NCT01272349	Acute intermittent hypoxia (low oxygen) vs. Room air (normal oxygen) placebo	18-65yr Age C6-T12 AIS C, D Ambulate (minimal assist) No sleep apnea Not receiving PT	Chronic SCI SCI>12m F/U 1wk	Began 10/2010 Atlanta, Chicago 40 subjects	Phase 1 RCT Double Blinded Placebo Controlled Crossover	Walking Performance (not specified)	Whether exposure to intermittent hypoxia will improve walking in ambulatory chronic incomplete SCI
Emory University NCT01272336	Acute intermittent hypoxia (low oxygen) vs. Room air (normal oxygen) placebo	18-65yr Age C6-C8 AIS C, D No sleep apnea Not getting PT	Chronic SCI SCI>12m F/U 1wk	Began 12/2010 Atlanta 40 subjects	Phase 1 RCT Double Blinded Placebo Controlled Crossover	Hand Grasp Grip Strength	Whether exposure to intermittent hypoxia will improve hand function in chronic incomplete tetraplegia

The above table is abstracted from the clinical trial registration website.

[www.clinicaltrials.gov](http://www.clinicaltrials.gov) using the search term “Spinal Cord Injury” and is updated quarterly (see [www.scopesci.org](http://www.scopesci.org)). Please refer to attached **APPENDIX C: Glossary**.

The table includes those trials from the search that: 1) are currently or soon-to-be *recruiting subjects*; 2) are *interventional* (tested an intervention/treatment) using *drugs, cell therapies, surgery, or hypoxia*; and 3) *targeted neurological or related functional improvement* as outcome measures.

Interventional clinical trials are routinely registered on [www.clinicaltrials.gov](http://www.clinicaltrials.gov) based on legal requirements\* and because scientific journals may require registration for publication of trial results. Investigators may choose not to register some early phase trials and those testing behavioral interventions are sometimes not registered, even though they may be important and scientifically rigorous studies.

\*U.S. Public Law 110-85 requires the registration and reporting of results of “certain applicable clinical trials,” i.e. controlled interventional clinical trials that are subject to FDA regulation and that involve a Drug or Biologic (other than Phase I investigations), or Device (other than small feasibility studies); <http://prsinfo.clinicaltrials.gov/fdaaa.html>.

### **Terms/Abbreviations:**

**NCT number:** trials registered with [www.clinicaltrials.gov](http://www.clinicaltrials.gov) are assigned a registration number that begins with NCT (e.g. NCT012345678). The number listed in the above table can be used in the search field to access the specific [clinicaltrials.gov](http://www.clinicaltrials.gov) webpage describing the trial, the study centers, and contact information.

**IV:** intravenous—administration of a drug by vein

**IT:** intrathecal—administration into spinal fluid overlying dorsal surface of spinal cord

**SQ:** subcutaneous—administration of a drug by injection beneath the skin

**F/U:** follow-up

**Phase 1/2:** phases 1 and 2 are combined with blinded assessment of clinical outcomes.

## APPENDIX B: What to ask before taking part in a clinical trial or human study? (your participation checklist)

Note: most of these questions should be answered during the informed consent process

Question	YES	NO	Additional Information
<b>1. Safety</b>			
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?			
<b>2. Possible benefits</b>			
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?			
<b>3. Clinical trial protocol</b>			
a. Is this 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 (Phase 1, 2, or 3) and what is the emphasis of study for this phase of the trial program?			
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?			

Question	YES	NO	Additional Information
<b>4. Payments and costs</b>			
a. Do I have to pay for this treatment?			
b. As a possible participant, are there other costs I have to pay to be involved in this study?			
c. Will my expenses associated with participating in this study be paid (e.g. travel to center for follow-up assessment)?			
<b>5. Participation in Other Trials</b>			
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 shown to be an effective therapy for my type of SCI by this clinical trial program, will I be eligible to receive this treatment later?			
<b>6. Preclinical or prior clinical evidence</b>			
a. Can you describe the preclinical or prior clinical evidence that indicates this experimental treatment might be beneficial?			
b. Have these findings been independently confirmed by other researchers?			
c. Are there any dissenting opinions and do these arguments have some validity for not going forward with this treatment?			
<b>7. Independent assessment of the treatment and investigator</b>			
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?			

## APPENDIX B (continued): 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 possible risks from either pre-clinical data 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. However, small the chances, there is always the possibility of some problem.

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 (clinical trial).

### 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.

### 3. 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 concerned (approach with caution).

b. *Can you describe what clinical trial phase this particular human study falls within (Phase 1, 2, or 3) and what is the emphasis of study for this phase of the trial program?*

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 or avoid. However, if this is a study involving people who have lived with a spinal cord injury for many months or years, you serve as your own control. Once again the investigators should be able to provide details immediately.

*d. Could I be randomly assigned to the control group?*

Answer: should be YES for Phase 2 and 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: This may be relatively short (days or weeks) or it could extend for as much as a year or more if the treatment is likely to change the course of your recovery over a prolonged period of time. Depending on the therapeutic intervention, it is possible that you may have to commit more time over the first few weeks and this may include hospital stay as an in-patient. Subsequently, you may be asked to return for assessments at defined times over the following months. Once you agree to participate, you should be willing to complete the full trial protocol, even if you feel you are not benefiting. Participants who withdraw from a study undermine the completion of the trial in a timely fashion and make it difficult to accurately interpret whether the treatment had any benefit.

*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 the investigators should ask you not to tell the examiners whether you are in the experimental or control group until the trial is over and the data is 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 to examine the effectiveness of a treatment and you should be suspicious.

#### 4. 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. You should be suspicious and probably should avoid the offered treatment.

*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.

## 5. Participation in other trials

a. *Will my participation in this clinical trial limit my participation in other SCI clinical trials?*

Answer: could be a possibility. The investigator should be able to outline which type of trials you may be excluded from in the future. For example, it is unlikely that participation in an acute treatment trial would later affect your potential participation to take part in a study at a later (chronic) time point. Nevertheless, the number of inclusion and exclusion criteria for any two trials is difficult to predict unless the protocols are known and compared.

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

## 6. Preclinical or prior clinical evidence

a. *Can you describe the preclinical or prior clinical evidence that demonstrates this experimental treatment is beneficial?*

Answer: the investigator should be able to outline the previous evidence, including the strengths and limitations of the treatment approach as defined by the preclinical (animal) or studies involving a related human disorder.

b. *Have these findings been independently replicated?*

Answer: this could go either way, but there should be some evidence that other researchers have obtained similar results when investigating this therapeutic target or treatments approach.

c. *Are there any dissenting opinions and do these arguments have some validity for not going forward with this treatment?*

Answer: the answer here is likely to be a qualified yes, as there are almost always some dissenting opinions about any proposed human treatment. Scientists are usually very critical of each other! The investigator should be able to provide you with a summary of the pros and cons for the treatment, but be wary of any treatment that is claimed to have no limitations. You, your friends and family will undoubtedly use the internet to look up information. We have provided you with a list of some of the reputable websites (Appendix D). If you run into biological or medical terms that you don't understand, we have tried to help by providing a glossary of some of the relevant terms (Appendix C). In any case, you should discuss your concerns and aspirations with your health care providers.

## 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 via the internet.



## APPENDIX C: Glossary of selected biomedical terms

**NOTE:** *These terms are commonly used in the discussion of spinal cord injury (SCI) and/or experimental treatments after SCI. They are provided for your reference, but we could not include every medical or biological term you might encounter.*

**Action Potential:** a short-lasting (~one thousandth of a second) event where the cell membrane potential (electrical difference across the cell wall) rapidly rises and falls. Action potentials occur in excitable cells, which include neurons, muscle cells, and some endocrine cells. Neuronal action potentials are conducted along an axon and are used to signal activation of that neuron. Action potentials are important for rapid cell-to-cell communication between neurons, especially over long distances, such as between the brain and spinal cord. Over long, large-diameter myelinated axons, action potentials can be conducted as fast as 425 kph or 265 mph (faster than most racing cars). Given the short distances involved in a reflex withdrawal (at most a few feet) it is understandable why it occurs so fast. In muscle cells (fibers) an action potential is the first event leading to contraction of the muscle fiber. Action potentials are also called "nerve impulses".

**Activities of Daily Living (ADL):** activities involved in self-care, sphincter management and mobility, such as bathing, dressing, eating, and other skills necessary for independent living.

**Ambulation:** walking, with or without the use of assistive devices such as a walker or crutches.

**Apoptosis:** see Neuroprotection

**ASIA (American Spinal Injury Association):** a North American based society of physicians, surgeons, scientists and other allied health professionals who treat or investigate SCI. For more information, see ASIA's website: [www.asia-spinalinjury.org](http://www.asia-spinalinjury.org).

**ASIA Assessment:** see below, International Standards for Neurological Classification of Spinal cord Injury (ISNCSCI).

**ASIA Impairment Scale (AIS):** (sometimes referred to as ASIA Grades) describes the completeness or severity of a spinal injury. A booklet and training manual is published and made available by ASIA (see above)

AIS A: no motor or sensory function below the neurological level of injury and all the way down to the end of the spinal cord (at the level of S4-S5 sacral segments). Also known as ASIA A

AIS B: some sensory function below the neurological level of injury, including S4-5, but no motor function. Also known as ASIA B

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

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

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

**Assistive, Adaptive, Supportive Devices:** a variety of implements or equipment used to aid individuals in performing tasks or movements.

**Astrocytes:** see Glia.

**Autonomic dysreflexia:** An autonomic reflex causing a sudden, severe, increase in blood pressure in response to noxious (painful) or innocuous stimuli, originating below the level of spinal injury. Autonomic dysreflexia is defined by an increase in systolic blood pressure greater than 20 mm above baseline systolic blood pressure. Symptoms can include headache, flushing (blushing), a stuffy nose, sweating above the level of the spinal injury, vasoconstriction (below the level of injury) and irregular beating of the heart. Autonomic dysreflexia can be triggered by an over-full bladder or bowel and is an ongoing medical complication, which occurs 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.

**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 moving).

**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](http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm) (also see Helsinki Declaration). Properly conducted clinical trials will adhere to the principles and guidelines of the Belmont report.

**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 (usually assumed to involve an overestimation of benefit and/or an underestimation of risk).

**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-blind studies: either the clinical investigator or the subject, but not both, are blinded.

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 procedures 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. Information regarding which treatment was assigned to each individual will typically be held securely by responsible independent members of the study center (or the central data center). It will not be matched with the data (trial outcomes) until after the study is completed, other than for the purposes of safety monitoring by an independent safety board.

also see: Open Label

**Burst Fracture:** is a shattering of the vertebra within the spinal column, usually the ventral round body of the vertebra (side of the column pointing towards the stomach). The bone shards may compress the spinal cord and there may be a risk of a fragment piercing the spinal cord. Surgeons will often undertake an operation to remove bone fragments and stabilize the spinal column with various rods and screws. The surgery is similar to the procedures performed to fuse (join) to vertebral segments together when a herniated disk is removed.

**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 at the lumbosacral level of the cord, often associated with lumbosacral vertebral or disc damage (also see: Conus Medullaris)

**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). also see information under Neuron, Glia, Action Potential, Synapse.

**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 statistical significance (and hopefully clinically meaning) of differences between the number of people 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 (placebo) control group. The endpoint may involve a measurement, a change in measurement, or the achievement of at least a certain level of change, pre-identified as a meaningful "response" for the treatment.

**Clinical Trial:** a human research program usually involving both experimental and control subjects to examine the effectiveness and/or safety of a therapeutic intervention. Prior to issuing a license for a new treatment of a disorder, a typical clinical trial program contains studies at three different stages or phases:

Phase 1 is to find out if the treatment is safe and subjects are given the treatment (often at slightly different doses) to see if there are any unexpected, harmful side effects.

Phase 2 is the second preliminary study designed to assess whether the treatment stimulates any positive biological activity within the target tissue or is likely to provide a clinically meaningful benefit for the intended body functions in the proposed subject population.

Phase 3 is the pivotal trial phase to test the effectiveness and safety of the therapy and involves the largest number of participants at multiple locations. If the treatment demonstrates a clear benefit with no serious side effects (adverse events), then it is eligible to be considered for approval by a national regulatory agency as a clinical treatment for the disorder being studied.

**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 when 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.

**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 a "freely moving" bundle of nerves within the vertebral canal and are called the cauda equina (literally, horse tail).

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

**Dermatome:** an area of skin innervated by peripheral sensory fibers which travel along a peripheral 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 to evaluate the preservation or loss of sensation throughout different parts of the body.

**Disk:** see Herniated Disk

**Dislocation:** a disturbance or disarrangement in the normal (overlapping) relationship of the vertebral bones of the spinal column (for example a facet joint dislocation).

**Distraction:** a term for the act of pulling apart the overlapping vertebral bones of the spinal column.

**Edema:** (or oedema) an accumulation of fluid, often occurring as part of the inflammatory process after trauma.

**Electrophysiological Testing:** the process of examining the effects (behavioral or electrical responses) to electrical, magnetic or natural stimulation of peripheral nerves or the CNS. Electrophysiological testing can be very informative for examining nervous system function, particularly the connectivity across the damaged spinal cord. See also Evoked Potentials.

**EMG (or Electromyography):** the recording of the electrical signals associated with the activity (contraction) of a muscle.

**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 ability of CNS pathways to conduct a sensory stimulus through the spinal cord and up to the surface of the brain. A Motor Evoked Potential (MEP) is the signal recorded from a peripheral nerve or muscle in response to an electrical or magnetic stimulation of the motor cortex (via the surface of the scalp) and tests the functional capacity of CNS pathways conducting motor (movement) commands.

**Frankel Scale:** an earlier scale for classifying severity of spinal cord injury that was modified in 1992 to create the ASIA Impairment Scale or AIS (see above).

**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 of specific peripheral nerves to train and enable a weak or paralyzed muscle to now make a functional and purposeful movement (e.g. phrenic nerve FES for breathing).

**Functional Independence Measure (FIM):** records the severity of disability in people after a disabling disorder based on 18 items. Thirteen items define disability in motor functions. Five items define disability in cognitive functions. FIM was not specifically designed for any single disability such as spinal injury. The spinal cord independence measure (SCIM) was designed to specifically record capacities after spinal cord injury (see below).

**Functional Recovery:** an improvement in the ability to perform a physical action, activity, or task. Some degree of functional recovery is expected to occur spontaneously after injury, but this may be very limited, particularly in sensorimotor complete (AIS-A) SCI.

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

**Glia:** usually non-impulse (no action potential) conducting cells of the CNS. Glial cells provide physical and metabolic support for neurons. Some regulate the internal environment of the brain, especially the fluid surrounding neurons and their synapses (connections), and provide nutrition to nerve cells. Glia have important developmental roles, guiding migration (movement) of neurons to their correct location 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. They remove dead or dying cells from the CNS. Oligodendrocytes form the myelin sheaths that surround (cover) axons. Myelin speeds the conduction of impulses (action potentials) along an axon, but myelin 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. Thus temporarily inhibiting myelin function is envisioned as a possible therapeutic target for spinal cord repair. Myelin surrounding the axons of peripheral motor or sensory axons is formed by Schwann cells, which do not inhibit axonal repair after injury. Schwann cell transplants have been thought of as a possible therapeutic strategy to facilitate repair after spinal cord injury.

**Good Manufacturing Practices (GMP):** set of regulations, codes, and guidelines for the manufacture of drugs (also known as active pharmaceutical ingredients, or APIs) and drug products (known as medicinal products in Europe), cells, 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, as well as quality control testing of pharmaceutical products.

**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](http://www.wma.net/e/policy/b3.htm) (also see Belmont Report).

**Herniated Disk:** the protrusion of one or more of the spinal disks, between the vertebra, into the spinal canal, thereby compressing the spinal cord directly or more often compressing one or more of the incoming or outgoing spinal 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](http://www.ich.org)).

**Incomplete SCI:** see Complete and Incomplete SCI

**International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI):** A detailed neurological assessment forms 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.

**Microglia:** see Glia.

**Motor Score:** based on the ISNCSCI assessment of muscle strength. The motor score is calculated by assigning to the muscle group, innervated and primarily identified with a specific spinal level, a score between 0 (no detectable contraction) and 5 (active contraction against resistance considered to be normal with a full range of movement about the joint). 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:** defined as the most caudal (lowest) spinal level as indexed by the key muscle group for that level having a muscle strength of 3/5 or greater while all key muscles above are normal (5/5).

**Motor-evoked potentials:** see Evoked potentials

**Myelin:** See Glia.

**Neurological Level of Spinal Cord 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 motor and sensory level and each of these segments is recorded separately. Note: the level of spinal column (bone) injury may not correlate with the neurological level of spinal cord injury.

**Neuron:** any of the impulse or action potential-conducting cells that constitute the brain, spinal cord, and peripheral nerves (sometimes called nerve cell). The number of neurons within the CNS is estimated to be about 100 billion. 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 such as synaptic inputs and conduct them toward the cell body), 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 between neurons are relayed across small gaps (synapses) by neurotransmitter chemicals released by an axon terminal across the synapse (junction between neurons or between a neuron and an effector cell, such as a muscle fiber). Large axons are insulated by a myelin sheath formed by oligodendrocytes or Schwann cells (see Glia).

**Neuropathic Pain:** usually perceived (felt) as a steady burning sensation or “pins and needles”, and/or as an “electric shock” sensation. “Ordinary” pain stimulates only pain nerves (nociceptive neurons), while neuropathic pain often results from the activation by innocuous (normally non-painful) stimulation such as light touch, warm, or cool stimuli. 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 hypersensitivity or allodynia.

**Neuroplasticity:** see Plasticity

**Neuroprotection:** the effect of any chemical, biological molecule or medical practice, which limits the degree of CNS damage resulting from primary mechanical trauma or a degenerative disorder. The majority of spinal cord injuries are the result of mechanical trauma. The neurons directly destroyed by mechanical trauma are probably lost forever, but in most cases the entire cord is not completely damaged by the initial injury. Protecting any surviving cells and neural connections is a high priority target.

Similar to when someone bruises the surface of their body, the initially disrupted spinal cells are known to release chemicals that can damage or destroy neighboring healthy neurons. This damage is known as secondary cell death (or apoptosis). Thus many experimental therapies are targeting the biochemical pathways responsible for secondary cell death and trying to limit their activity after spinal cord trauma. One of the limitations may be the need to stop these biochemical reactions within a very short time frame after the primary trauma (perhaps within a few hours). This is a difficult window of opportunity for a therapeutic intervention and also challenges the treatment of other CNS disorder such as traumatic brain injury and stroke.

**Nutraceutical:** Patients have claimed benefits from alternative medical approaches although there is often limited or no documented scientific evidence to support these claims. Nutraceuticals are non-drug (non-prescription) substances (for example, herbal medicines) that are produced in a purified or extracted form and are administered orally to provide compounds, which are intended to improve health and well-being. These substances are not always controlled or approved by a government health regulatory agency prior to or after sale. If properly labeled, they will usually have a disclaimer stating the product does not guarantee an improved health benefit. Nutraceuticals are often associated with naturopathic or alternative medicine, as is acupuncture.

**Oedema:** See Edema

**Oligodendrocyte:** See Glia.

**Open label:** both the researcher and the trial participant know the treatment that the participant is receiving. See also: Blinded assessments.

**Pain:** See Neuropathic Pain

**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 lower extremities (legs). This implies damage to the spinal cord below the level of T1 and may include damage to the conus medullaris or cauda equina.

**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's research and claims have achieved rigorous scientific and statistical standards.

**Pharmacodynamics:** the study of the biochemical and physiological effects of drugs in the body and the mechanisms of drug action, including the relationship between drug concentration and effect (in brief - what the drug does to the body).

**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. These 4 outcomes are often noted by the acronym ADME (in brief, what the body does to the drug).

**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. spinal cord injury) or examination of appropriate target cells in an *in vitro* culture situation.

**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 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 benefits of an inactive substance from any physiological effects due to the active (experimental) treatment.

**Plasticity:** refers to behavioral changes that occur in the organization of the CNS. Neuroplasticity can be either positive or negative. For example, the emergence of autonomic dysreflexia or neuropathic pain can be viewed as negative changes that occur after spinal cord injury. Whereas the strengthening of synaptic connections and axonal sprouting after spinal cord injury (SCI) are changes that might lead to the formation of new neural circuits that permit the recovery of some motor function. Experiments have demonstrated improved neuroplasticity with the physical and occupational training found within active rehabilitation programs.

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 or spinal cord 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.

**Prospective:** 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 human study. 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 and analyzed prospectively (in a go-forward manner).

**Quadriplegia:** 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 or Randomized Control Trial:** a clinical trial in which the subjects enrolled are randomly assigned to either the experimental treatment arm (group) or control 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). Well-designed RCTs minimize the influence of variables other than the intervention that might effect trial outcomes. For this reason, they provide the best evidence of efficacy and safety. The most rigorous RCTs utilize a placebo (inactive) control group and blinding (conceal from trial examiners which participants have received active vs. control treatment) to minimize bias in interpretation of results.

**Regeneration / Repair:** terms used to describe mechanisms underlying restoration of function. In the case of CNS damage such as spinal cord injury, regeneration has been used to describe the regrowth of axons severed during spinal trauma. It was once thought that effective recovery after a cervical cord injury could only be accomplished when injured axons regenerated over long distances to the end of the cord (lumbosacral regions). It is now believed that short distance axonal sprouting across the zone of injury can be equally effective as functional “plasticity” (re-wiring) within the neural circuits below the level of injury can contribute to recovery. Repair is a more inclusive term and includes many processes that could contribute to recovery of function, including: “drugs” that stimulate axonal sprouting or the generation of new replacement cells from within the cord, the transplantation of “stem” cells, as well as beneficial reactions from CNS glia after spinal cord damage and implanted bio-compatible scaffolds.

**Secondary cell death:** see Neuroprotection

**Sensory Score:** based on the ISNCSCI assessment of the patient's perception of sensation from the skin of the body. The sensory score is calculated by testing a point on the (skin surface) dermatome associated with each spinal level from C2 to S4-5. This is done for both light touch and pinprick sensation and in comparison with sensations perceived from the skin above the level of spinal cord injury, such as the face. Each point is assigned a score from 0 (absent sensation) through 1 (impaired or 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]

**Schwann Cell:** See Glia. [p.25]

**Spinal Cord Independence Measure:** (or SCIM) 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 (currently in version 3). The SCIM is a 100-point disability scale developed specifically for SCI with emphasis on 17 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.

**Sham operative procedure:** a surgical procedure in which the subject is operated on but does not receive the experimental intervention. This is the equivalent of a drug placebo treatment.

**Somatosensory evoked potentials:** see Evoked potentials

**Spasticity:** involuntary increase in muscle tone (tension) that occurs following damage 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.

**Stem or Progenitor Cells:** Cell transplantation has been extensively reported by the popular media as a universal treatment for all manner of illness or injury. While tremendous progress has been achieved for certain simple tissues and their associated disorders and diseases, including bone, muscle and blood, the routine use of cell transplants for CNS disorders is still in early development. Unfortunately, because generating cells for transplantation is a relatively easy procedure, several unscrupulous clinics have been offering surgical treatments with cell injections, even though there is no validated evidence for benefits from these procedures.

As can be appreciated the CNS is the most complex organ of the body containing thousands of uniquely identifiable cell types. Most transplanted cells are likely to only differentiate (change into) a few types of adult neurons and glia. Thus what type of cells and how many cells should be transplanted are still unanswered questions. When do we transplant after injury, where do we transplant and how do we protect the transplanted cells from being rejected by the host CNS. Every simple answer triggers dozens of further questions. What follows is a very short and incomplete explanation (for further details, please consult documents available on the International Spinal Cord Society (ISCoS) website ([www.iscos.org.uk](http://www.iscos.org.uk)))

'True' stem cells have the potential to self-renew indefinitely and differentiate (develop) into numerous types of cells. In practice most cell transplants do not involve 'true' stem cells. In reality, they are progenitor cells, which come from stem cells. However the term stem cell has entered popular folklore and is commonly used for all transplanted cells. Progenitor cells have less plasticity than 'true' stem cells and a more limited capacity to differentiate. Once CNS cell transplant procedures have been developed and refined, the potential benefits of stem cells are numerous and include: replace lost cells due to injury or disease, provide substrate or scaffold for axonal outgrowth to create novel neural connections, limit detrimental inflammation and reduce secondary cell damage, promote blood vessel formation, and/or release beneficial cytokines and growth factors. Of course, with any emerging technological advance there a number of unknowns or concerns with a premature application of cell transplants after spinal cord injury and these include: a very incomplete understanding of the benefits and risks in preclinical animal studies, poorly defined cell products (some with no GMP protocols or standards), additional damage to cord if cells have to be injected directly into the spinal cord tissue, stimulation of neuropathic pain, and/or causing the formation of cancerous tumors since some stem or progenitor cells can rapidly divide.



**Surrogate endpoints:** A measurement of an expected biologic activity from the experimental drug or cell transplant that substitutes for the clinical (functional) endpoint. A surrogate endpoint (outcome) may predict a patient's final clinical outcome. A surrogate marker (measure) may indicate whether a drug is effective without having to wait for the longer-term functional clinical endpoints being achieved.

The identification of an accurate surrogate measure or marker can reduce the time required in an early clinical trial phase to show a possible benefit. Surrogate endpoints can and have been used in Phase 2 clinical trials.

**Synapse:** the cell membrane of the signal-passing neuron (presynaptic neuron) comes into close apposition with the membrane of the target (postsynaptic) neuron. Both the presynaptic and postsynaptic sites contain receptors and molecular machinery necessary for synaptic communication between the two neurons. The presynaptic part belongs to an axon terminal, while the postsynaptic element is usually a dendrite or soma of the second neuron. It should be noted that many neurons can receive and integrate inputs from thousands of presynaptic neurons and project to several hundred other neurons. In short, every neuron is presynaptic to some neurons and postsynaptic to other neurons. In a chemical synapse, the presynaptic neuron releases a chemical called a neurotransmitter that binds to receptors located in the postsynaptic cell, usually embedded in the plasma (cell) membrane. The neurotransmitter may activate a receptor-ion channel complex directly or an indirect second messenger pathway that either excites or inhibits the postsynaptic neuron. The number of neurons is estimated to be 100 billion and the number of synaptic connections in the average adult brain is truly astronomical and defies comprehension (approximately 250-500 trillion).

**Tetraplegia:** (also known as quadriplegia) refers to loss of motor and/or sensory function in all four limbs due to spinal cord damage, with impairment of the upper extremities as well as trunk, legs and pelvic organs. This implies damage to the cervical spinal cord (at or above the T1 level). Technically tetraplegia is the more correct term, because "tetra", like "plegia", has a Greek root, whereas "quadra" has a Latin root and in classic naming terminology you do not mix Latin with Greek words!

**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).

## **APPENDIX D: Selected websites** (listed alphabetically)

***NOTE:*** each site has multiple links for further information

Academy of Spinal Cord Professionals (ASCIP): <http://www.academyscipro.org>  
 American Spinal Injury Association (ASIA): <http://www.asia-spinalinjury.org>  
 CareCure Community: <http://sci.rutgers.edu>  
 China Spinal Cord Injury Network: <http://www.chinasci.net>  
 Christopher and Dana Reeve Foundation: <http://www.christopherreeve.org>  
 Craig H. Neilsen Foundation: <http://www.chnfoundation.org>  
 elearnSCI (online information on SCI care and treatment ): <http://www.elearnsoci.org>  
 European Multicenter study about Spinal Cord Injury (EMSCI): <http://www.emsci.org>  
 European Spinal Cord Injury Federation: <http://www.escif.org>  
 EuroStemCell: <http://www.eurostemcell.org>  
 Fondation internationale pour la recherche en paraplégie (Switzerland): <http://www.irp.ch>  
 Institut pour la Recherche sur la Moëlle épinière et l'Encéphale (France): <http://www.irme.org>  
 ICORD (International Collaboration on Repair Discoveries): <http://www.icord.org>  
 International Society for Stem Cell Research (ISSCR): <http://www.isscr.org>  
 International Spinal Cord Society (ISCoS): <http://www.iscos.org.uk>  
 International Spinal Research Trust: <http://www.spinal-research.org>  
 Japan Spinal Cord Foundation: <http://www.jscf.org>  
 Miami Project to Cure Paralysis: <http://www.themiamiproject.org>  
 Neil Sachse Foundation: <http://www.nsf.org.au>  
 NINDS Spinal Cord Injury Information Page: <http://www.ninds.nih.gov/disorders/sci/sci.htm>  
 Paralyzed Veterans of America: <http://www.pva.org>  
 Rehab. Research & Train Center (RRTC) on Secondary Conditions (USA): <http://sci-health.org>  
 Rick Hansen Foundation (Canada): <http://www.rickhansen.com>  
 SCIRE (Spinal Cord Injury Rehabilitation Evidence): <http://www.scireproject.com>  
 SCOPE (Spinal Cord Outcomes Partnership Endeavor): <http://www.scopesci.org>  
 Spinal Cord Injury Canada: <http://www.spinalcordinjurycanada.ca>  
 Spinal Cord Injury Network (Australia): <http://spinalnetwork.org.au>  
 Spinal Cure (Australia): <http://www.spinalcure.org.au>  
 United Spinal Association (USA): <http://www.unitedspinal.org>  
 Wings for Life: <http://www.wingsforlife.com>

## APPENDIX E: Selected references

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