Experimental Treatments for Spinal Cord Injury: What you Should Know

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Introduction

Experiencing a spinal cord injury (SCI) is extremely distressing, both physically and psychologically, and throws people into a complex, unfamiliar world of medical procedures, terminology, and decision making. 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 an SCI, patients are often told that there are no approved drug or cell transplant treatments that will repair the damage and restore voluntary movement. This is still true, regardless of what you may hear or read about a research "breakthrough." 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. Treatments that could one day improve the function of people living with SCI are being tested. However, there are also people who might offer you an unproven treatment, claiming they can restore function if you have money to pay!

This article is intended to address some of the questions you may have about various therapies or treatments after SCI, that are experimental, meaning their benefits and risks are still unproven but they are being studied by medical experts and researchers. The therapies discussed in this article are not to be confused with the approved medications that you might receive to manage infections, spasticity, or other health issues. The information provided focuses mostly on testing of new drugs, cellular therapies, tissue or cells used as grafts, antibodies or other biological substances, and newly developed technologies and devices. It offers advice to help you make an informed decision about participating in a clinical trial. It will also explain why you should avoid paying for unproven treatments and placing yourself at risk for an unlikely benefit. You are encouraged to discuss these issues with your healthcare team.

A group of leading scientists and clinicians contributed their time and expertise to create this article to help you understand how treatments are developed and tested and to help you make informed choices. It was first created in 2006, revised in 2012, and has now been updated as of 2021.

The first thing to understand is how experimental treatments become proven therapies that you can be confident might help you.

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What is the difference between a clinical trial and clinics offering unproven procedures?

The process by which science becomes approved medical practice is designed to minimize harm and maximize benefit to patients. This is a long but well-defined process meant to protect people and determine who is most likely to benefit from a new therapy. New drugs or cell-based therapies first tested in animal studies can appear to be very promising. However, they need unbiased, well-constructed clinical trials to show they do not pose unacceptable risks and do benefit people with a specific injury or disorder. Unregulated use of new, unproven treatments based on unreliable evidence raises false hopes and can endanger people. Offering unproven therapies, not authorized by national or local regulators, in exchange for payment hijacks the processes meant to protect patients. It can result in patients spending large sums of money for no benefit, and some even experiencing serious complications (more on that later). That is why it is really important to understand if an experimental procedure is part of a well-designed and scientifically justified (i.e., valid) clinical trial before you consider receiving it.

How do I tell whether an experimental treatment is part of a valid clinical trial program?

You are curious, but hopefully cautious, and wish to know how to best evaluate the credibility of a new treatment or a clinical trial. It can be difficult to tell the difference between a genuine clinical trial and a treatment program that only claims to be a trial. Perhaps the easiest way to tell the difference is whether you must pay for the treatment being studied. If you are asked to pay to receive a drug or procedure that is still experimental, it is not a clinical trial! You should not be asked to pay for the experimental treatment itself. However, even in a valid trial you might have to cover standard care and accessory costs such as travel or rehabilitation, or your insurance may be charged (and your usual copayments or deductibles might apply).

Even though treatments that can restore the function lost after SCI have not been established yet, several clinical trials are being conducted under the watchful eye of governmental regulators. A website, SCITrialsFinder.net, has been developed to explain and make it easier to find and understand SCI clinical trials that are being conducted carefully and safely.

Before agreeing to participate in any well-run clinical trial, you must be fully informed about the trial and what you can expect. This means in terms of the treatment, follow-up appointments, etc., and formally consent to participate (see "informed consent" below). There are questions you should ask and answers you should expect from someone explaining a clinical trial or offering an experimental treatment. The differences between a rigorous clinical trial and an unproven "treatment" offered by a clinic claiming success of their new, "cutting-edge" therapy can be confusing. Appendix A will help you ask the right questions and understand the answers.

Why are clinical trials necessary?

Every experimental therapy and clinical trial, without exception, has at least some risk of causing unintended complications or other potential harm to participants. Well-designed trials must consider and document both benefits to those who receive treatments and also unforeseen risks. It can be surprisingly difficult to prove if a treatment or therapy is safe and that it really works. If a person receives an experimental therapy and experiences some recovery, they commonly believe they got better as a direct result of the new treatment. However, the improvement may not have been the direct result of the treatment. There are two other possibilities to consider.

Spontaneous recovery and the importance of rehabilitation. Immediately after an SCI, some people are completely paralyzed below the area of injury. Even without restorative treatment, almost all will experience at least a little improvement in function (spontaneous recovery), which can be enhanced by active rehabilitation. Depending on the amount of damage to the spinal cord, some people recover more function, and a small number of people will achieve dramatic recovery. The rate of recovery is usually greatest over the first 3 months, but with sustained rehabilitation and effort, functional improvement can continue for a year or even more.

Controversial "medical tourism" clinics that offer cell transplants to people may also include vigorous rehabilitation. Thus, for people who have received an unproven drug or cell transplant, it can be difficult to tell whether improvement is due to some spontaneous recovery, to the benefits of rehabilitation, or to the effect of the experimental treatment itself. Clinical trials are designed to determine which of these possibilities can most reliably explain 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 report outcomes that are not the direct result of a therapy. Thus, even after receiving a control substance, one that contains 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 an apparent benefit when the improvement is due to some other cause.

A control group in a clinical trial is designed to equalize all factors and expectations that could affect outcomes, other than the treatment that is being tested. This means that by comparing two or more groups of people, scientists will truly see the effect of the experimental treatment. A placebo or "sham" treatment is given to a group of control subjects who otherwise get all the same testing and care as the experimental group, without letting either the patients or the clinicians know who is receiving the active treatment and who is not. While not always feasible, this is the most effective way to accurately measure whether there are actual benefits of the experimental therapy. In a trial, control patients who receive a placebo might report improvement in their condition, sometimes as much improvement as the group who received the active treatment. When that happens, it is only logical and reasonable to conclude the experimental treatment has little or no therapeutic benefit.

If an experimental therapy has not completed a properly designed clinical trial program, there is a real danger that treatments that do not actually work or even do harm could be offered. This puts patients at risk, and can interfere with the development and testing of safer, more effective treatments.

What makes a good clinical trial?

A good (scientifically sound) clinical trial (human study) usually will test an experimental "therapeutic" (a drug, cell therapy, device, etc.) only after it has undergone extensive study in animals, or in people with another related human disorder, and will have published evidence of safety and a potential for a beneficial effect. Such 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. New surgical and rehabilitation strategies are also tested to show safety and that people benefit from the procedures, but some trial aspects, like sham procedures, may not be feasible or ethical in these cases. Without completing a clinical trial and comparing the effects of a treatment in the experimental group to the outcomes in those who do not receive the treatment, it is impossible to determine if the treatment safely provides a meaningful benefit.

Unintentional bias or self-interest on the part of the people who conduct clinical trials (investigators) 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. Clinical trials are designed to protect from this bias and be as fair as possible in assessing the effect of a treatment.

Blinding. When testing a new therapy that shows promise, people with spinal injuries, their surgeons, therapists, and everyone involved in SCI healthcare wants the treatment to improve independence, mobility, and quality of life. These genuine and compassionate desires can result in unintended biases and lead people to overestimate functional improvements or overlook possible risks. Therefore, it is best to "blind" both the trial participants and the investigators, ensuring they do not know which person received what treatment (experimental or placebo control).

Sometimes the persons administering or receiving a treatment must know who does or does not receive it. For example, surgeons will know what procedure they perform, and people who receive a new form of rehabilitation will, of course,

know that they are in the experimental group. In these cases, at minimum, other study personnel who collect or analyze outcome data can and should be "blinded" so they do not know what treatment was administered to the trial participant they are examining.

Conflict of interest. Although clinical trial investigators may be reimbursed for their research, they should not have a direct financial benefit or other competing interests in the outcome of the trial. If an investigator could benefit financially from the outcomes of a human study, this is a conflict of interest that could be a temptation or unconscious bias to report a positive benefit of the treatment. Such conflicts can and should be carefully managed. Institutional Review Boards are independent panels that safeguard patient rights and must approve scientific clinical trials. They 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.

Avoid unproven treatments offered for direct payment. Understandably, some patients with an SCI want to improve, no matter the cost. That creates 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 scientifically valid clinical trial programs. Depending on your health care coverage, you, your private 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, and your usual deductibles and copayments may apply. You should ask and be told up front what, if any, payment is required for your participation in a trial, but the experimental treatment itself and all the related follow-up assessments should be provided at no additional cost to you.

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 not be effective or even do harm. We strongly advise you to only participate in well-designed SCI clinical trials where there is solid evidence of positive benefits from previous animal experiments or approval by regulatory agencies of the treatment for a related clinical disorder. Treatments are approved for specific groups of people with particular disorders, so they are not yet proven to be safe and effective in other populations. That is why there would be a need for a new clinical trial focused on people with SCI.

How are clinical trials structured?

An important part of most clinical trials is the assignment of participants to either an experimental treatment group or a control group, which is often done randomly to prevent bias. As mentioned above, the control group goes through similar procedures but does not receive the experimental therapy. This helps eliminate the possibility that many uncontrollable factors and experience of being part of a study could influence the participants' outcomes.

Random assignment to either the experimental or control group 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, any observed improvement seen after receiving an experimental treatment therapy combined with rehabilitation could be falsely attributed to the treatment itself.

In some cases, participants with chronic SCI have a very stable baseline level of function that can be measured before they receive the experimental therapy and then compared to their capabilities later in the trial to see if there is any improvement. This exception to the use of a separate control group can only be made if the trial is carefully designed so that the participants act as their own control without introducing bias into the results. In some trials, two groups are tested, one group receiving the experimental treatment followed by a period in which they receive a placebo, while the other group receives the placebo first, followed by the

experimental treatment. Regardless, the examiners assessing the outcomes in such trials are blinded as to what was done and in what order.

Another exception relates to early clinical trials (Phase 1; see below for description of trial phases), which primarily focus on testing the safety and the feasibility of 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 later Phase 2 or Phase 3 trials that test whether the treatment actually provides a benefit (efficacy).

As mentioned above, it is also important to remove bias either trial investigators or study participants may have. This is why trial programs that successfully pass Phase 1 safety evaluation need to be followed by trials designed to examine the true effect, where the investigators are blinded as to which group gets the experimental therapy to preserve the objectivity that is needed to accurately determine whether a treatment is safe and beneficial.

What if I get assigned to the control group?

Most people with high hopes 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 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 to be effective, it would be unnecessary and unethical to delay treatment by further testing.

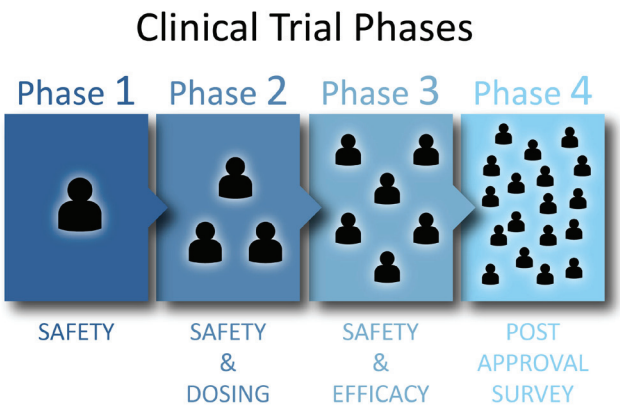
By definition, ethical trials are conducted because the true benefit of experimental treatments is not known. Clinical investigators have to adopt a "wait and see" perspective about the risks and benefits, until all trial phases are completed. If by mischance the treatment has an undesirable or harmful side effect, then being in the control group may be an advantage! You should also consider that being in the control group will come with some added benefits such as more contact with the professionals and more thorough examinations that are not necessarily part of the standard care.

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 receiving the tested treatment after the trial, if it is proven to be effective and if you still meet the eligibility criteria. If this is not made clear to you, you need to ask about it.

What are the various trial phases?

Clinical trials testing drugs, cell therapies, antibodies or other biological therapies, and some new devices usually require positive results in three separate phases (Phase 1, 2, and 3) before an experimental treatment will be approved by a government regulatory agency for use in people with a specific disorder (**Figure 1**). Each trial phase is more demanding than the previous one, involving more participants and longer term outcomes that demonstrate real benefit to people with that disorder, as well as long-term safety. 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 will be participating.

Phase 1 is to find out if the treatment is safe and can be tested in humans. 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 it is common not to have a control group, as the emphasis is on safety and tolerability of the experimental treatment. Such trials are sometimes referred to as "open label" trials as everyone (participants and investigators) knows who gets the treatment and there may not



be 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, but conclusions will not usually be made about the benefit of the treatment. It should be noted that safety is always monitored throughout all clinical trial phases, but in Phase 1, it is the main focus.

Phase 2 is a second round of trials designed to assess whether the treatment stimulates the predicted positive biological activity within the body or a specific area (target tissue) or provides a clinically meaningful benefit by improving the intended body function(s). These outcomes in the experimental group are compared to those of a control group that receives 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 assessments to detect and measure any positive (or negative) effects of a treatment. This phase is important to establish the best protocol for the next phase, a pivotal Phase 3 study. Even if the evidence from Phase 2 studies suggests a possible benefit in some of the participants, this still does not prove that the treatment will be reliably effective for others. The number of participants is still relatively small, and particularly good or bad results in just a few participants can lead to misleading conclusions.

Phase 3 is the pivotal trial phase, designed to more fully test the effectiveness and safety of the therapy. It 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 related to treatment) then it is eligible for consideration of approval by a national regulatory agency as a treatment for the disorder being studied in the trial.

What are regulatory oversight and registration of clinical trials?

Scientifically valid clinical trials should be conducted under the oversight of appropriate national and local regulatory authorities. National authorities such as the Food and Drug Administration (FDA) in the United States, the European Medicines Agency (EMA), or Health Canada (HC) regulate trials testing new drugs, cellular therapies, tissue transplants, and new devices or technologies. Trials that test surgical procedures or rehabilitation activities may not be regulated by those agencies, however, all genuine trials are overseen and should have approval from the local human research ethics committee (such as an Institutional Review Board or IRB).

It is also important to remember that drugs, cells, and devices are approved to treat specific disorders, or segments of the population. Off-label use (e.g., for people with other disorders, another age group, pregnancy, etc.) is still a form of unproven therapy. Any scientific studies of these treatments should be done with the oversight of the proper authorities. Not only is this safer for the people that receive the therapy, but it is the only way a treatment can gain acceptance as a standard of care for those other disorders or populations.

An increasingly common practice is the registration of trials on a publicly available site (e.g., http://www.clinicaltrials.gov, https://www.who.int/clinical-trials-registry-platform, https://anzctr.org.au/). Registering the trial on databases such as these is important, but it is not an assurance that the trial has received the go-ahead from the proper national (FDA, EMA, HC) or local (IRB) oversight.

The ClinicalTrials.Gov website can serve as a source of valuable information for patients, clinicians, and scientists, but it may be difficult for lay-people to follow. SCITrialsFinder.net can help you navigate this information more easily. The physician investigator asking you whether you wish to participate in a clinical trial will provide proof that all national and local regulatory and ethical human study approvals have been obtained.

What is required for participation in a clinical trial?

Before anyone can be enrolled in a trial, they must receive a full, understandable explanation of what

the trial and their participation will involve. This process, known as "informed consent" is explained below. Next, they are screened against a set of pre-set criteria to see if they qualify to participate in that clinical study. Not all people with the disorder will qualify to participate in a given trial. Every trial should have specific conditions (called inclusion/exclusion criteria) that must be satisfied for an individual to participate. Experimental therapies are designed to treat certain conditions and situations, so trials are designed to include participants that have those conditions and are at least risk for harm and most likely to benefit from the therapy being tested. For example, the past evidence may indicate a drug or cell transplant should be administered within a specific time window after SCI, so enrolling you if you are not in that stage of injury could put you at risk when benefit is unlikely. The location and severity of your SCI may or may not meet the eligibility requirements because of where and how the treatment is thought to act, the specific outcomes being measured, or other conditions (e.g., diabetes, epilepsy, etc.) that would limit your suitability for participation or for proper evaluation.

When an experimental treatment is being tested 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 participants can make it difficult to show that a treatment has a real benefit. Like many neurological disorders, SCI can result in varying degrees of impairments, and you have probably already been told that your injury is classified as being at a certain level of your spinal cord and along a scale extending from complete sensory and motor loss to incomplete, or even minimal, sensory or motor loss. If we were to put all the different injury types of people with SCI into one study, it is likely that the different degrees of impairment and spontaneous recovery would make it impossible to determine whether an experimental therapy was beneficial. This is why clinical trial programs are often repeated for specific subtypes of a disorder or disease. Not qualifying for a trial does not necessarily mean that you would not ultimately benefit from the treatment being tested. Therefore, you might be able to obtain it later, if it is successful and likely to benefit someone with your type and stage of SCI.

What is informed consent?

Should you meet the eligibility requirements to participate in a clinical trial, you will be asked to give your informed consent. This involves a discussion with a trial investigator where:

1. The nature of the experimental therapy should be 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 if you will be randomly assigned to either the experimental treatment group or the placebo control group and if your treatment group will not be disclosed to you until the study ends and is unblinded.
4. If a trial does not include a control group, you should be told why. Is it the phase of trial or the type of intervention? And what else is being done to ensure the results are fair and unbiased?
5. You should be informed of all study procedures, the duration of your participation, and what is required of you for follow-up visits.
6. You should be informed how the cost of any standard clinical care or rehabilitation, training, or other activities associated with the trial (including travel costs), will be covered.
7. You should be told if you will receive compensation for your participation in the trial and reimbursement for your expenses.
8. You should be told how any treatment or compensation for possible research-related injury will be arranged and who will pay for it.
9. You should be told how any medical complications you might experience will be handled and who will cover those additional costs.
10. You should be informed of the alternatives to participation in the clinical trial.
11. You should be informed of your right to withdraw from participating 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.
12. You should be given adequate time to ask questions and be fully satisfied that all your questions have been answered.

One way to judge the quality of a clinical trial is the thoroughness of the informed consent process, the care and time that is taken to fully explain that you may or may not get any benefit from the treatment, and, especially, a description of all significant risks. This is particularly important when the long-term effects of a treatment are not well understood.

What if I have already received an experimental therapy?

People who have already participated in a previous clinical trial and received an experimental therapy for SCI (approved by regulatory authorities or not) may or may not be eligible to participate in another trial. The reason for this is that a previous therapy may have altered the person's natural recovery and/or connections within the spinal cord in undetected ways, making it difficult to fairly test 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. Even if you were not accepted as a participant in a trial, you may be able to receive that treatment if and when it is approved as a treatment for SCI, and if it could benefit people like you (the approval will specify what age groups, genders, and types of injury the treatment is proven to benefit, e.g., acute versus chronic SCI).

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

After the informed consent process is complete and you have formally volunteered as a participant (enrolled), you are likely to be assigned to either the experimental treatment group or a control group. This assignment is likely to be a random process based on the rules of the trial, and you may or may not know whether you will receive the experimental treatment or the control treatment. Remember, blinding is important to objective results. If the trial is blinded, after the trial results have been analyzed, you can ask to find out what you received. Participation will include 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 during the informed consent process, but you can feel free to ask about them at any time.

Most trials require you to volunteer several hours of your time 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 of your capacity to perform activities of daily living. Imaging studies such as MRI may be carried out, and tests to study the connections within your spinal cord (conduction studies) may require electrodes to be placed on your skin so electrical activity can be measured. 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, and you should be reimbursed for travel and accommodation expenses if they are needed.

What should I expect after a SCI clinical trial?

As of this writing, there is still no approved effective treatment that restores neurological function 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. Recent trials have revealed that surviving neural connections might be activated by treatments like electrical stimulation, but even 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 happens little by little, 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.

What treatments are available now?

Surgical procedures. People with SCI should undergo appropriate surgical procedures, if medically fit for the surgery, when 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 regrowth, and reduce the likelihood of further SCI in the future. During this procedure the abnormal pressure on the spinal cord and spinal nerves should be reduced, maximizing the potential for recovery. For more details on these and other treatments, please see http://www.elearnsci.org.

Rehabilitation strategies and assistive devices. Many SCI are incomplete and 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 could be retention of some sensory feeling (e.g., detection of a pin prick) or ability to move some muscles (e.g., 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. These build upon and extend remaining functions, including repetitive voluntary movement training, strength training, and constraint use therapy (e.g., where someone is prevented from using their better functioning arm to force the use of the weaker one). 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 agreement that active rehabilitation after SCI is important and effective in preserving body functions, as well as improving the recovery of functional activity. 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 by a therapist or caregiver of a person's limbs through its entire normal range of motion. Passive rehabilitation is likely to be a part of any treatment protocol, but is unlikely to be sufficient to maximize functional outcomes after SCI.

Overall, most healthcare providers believe that any active rehabilitation is better than no rehabilitation. 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.

Once again, if an individual is medically stable and will not suffer any negative effects due to the movements associated with the therapeutic activities, then rehabilitation training can be started soon after SCI. There are an extensive number of activity-dependent rehabilitation studies and trials underway. Although there are too many to cover here, scireproject.com provides detailed discussions of the strengths and limitations of the many rehabilitation strategies; please consult the SCIRE (Spinal Cord Injury Rehabilitation Evidence) chapters, which are available as a free download (www.scireproject.com/). Do not hesitate to discuss active rehabilitation strategies with your therapist and/or physician.

Drug and other therapies. Several 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. As mentioned above, SCIREproject.com presents the published evidence for SCI treatments that have gone through clinical trials. Your health care professionals can advise and guide you. SCIREproject.com/community/ provides information about SCI research that is written in everyday language.

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? 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 cells to keep them from dying in the hours or possibly days following the injury
- 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
- Repair/Regeneration: reducing long-term damage to the injured cord, promoting new growth and connections from spinal neurons, possibly replacing lost cells to rebuild the damaged spinal cord
- Replace/Assist function: using 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, and a few are already in early stage clinical trials (for more details visit SCITrialsFinder.net).

Should I still consider receiving an unproven treatment outside of a clinical trial?

You now possess the knowledge to understand why the efficacy of a potential treatment can only be assessed with the right tools, meaning a properly designed set of trials. If you still plan on receiving an unproven and inadequately tested treatment at a clinic claiming success, you need to consider that you will pay for a treatment that will most likely bring you no improvement. However, you must also consider your safety and possible adverse effects. These are usually not tracked at such clinics or reported to regulatory authorities so you should be very cautious; claims that an experimental treatment has no risks should raise your suspicions.

You might feel there is nothing to lose from trying something new, even if it is not proven. Unfortunately, most of the unproven treatments for sale throughout the world carry very little likelihood of actual benefit, very real risks, and at high financial costs. Complications may create new health problems. Those might be transitory, but there is a chance of losing further functions, causing pain or even life-threatening problems. In a number of cases, independent observers have later reported serious complications in some of the people who received unproven treatments. For example, there are now several reports of patients who developed a tumor after receiving an experimental stem cell transplantation into their spinal cord (Dlouhy BJ et al., 2014; Woodworth CF et al., 2019). A survey of a large group of neurologists (Julian K et al., 2020) in the United States found that "complications of stem cell tourism can be severe, and they are under-reported." There are some published reports available that you can read and discuss with your healthcare providers.

What if I read about it in the media?

It can be hard to tell the difference between a clinical trial being conducted responsibly and a clinic trying to sell you unproven treatments. One thing to look at is the way the treatment is marketed. Unproven treatments are usually advertised directly to patients, often through persuasive language on the clinic's website, Facebook, or other media platforms. These clinics frequently overstate the benefits of their treatment and use patient testimonials to support their claims rather than trial results published in clinical journals. As we described earlier, perceived improvement may be due to other factors than the advertised treatment, such as an intense belief that it will work, intensive

rehabilitation, healthy lifestyle changes adopted along with the treatment, or other factors. One should question such hand-picked testimonials and consider how biased a view they present.

You might also read about the great promise of a new laboratory finding, saying a drug or cell therapy helped animals with spinal injuries. These are important findings, but a long way from changing clinical practice. There are many steps remaining to learn whether these could be safely tested in humans and determine if they are effective in helping people with SCI. During testing, the new therapy might need to be significantly refined, and in the end, it may be discovered that it has some benefit but comes with unacceptable risks. As much as successes in the laboratory are welcome, it is a mistake to jump too quickly to assuming they will lead to a new therapy.

Where can I get good advice?

Reliable information is always the goal. You have a number of avenues you can explore. Whatever path 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 kinds of websites, which provide a variety of information. There are several professional societies, nongovernmental 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 SCIs.
- 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. Earlier versions of this article had a more extensive discussion of the above topics (some might say too detailed a description). However, the 2012 version is still available at the ICORD website (http://www.icord.org).
- You can find up-to-date information about ongoing clinical trials by visiting SCITrialsFinder.net.

Disclaimer

This guide is based on published scientific papers and the professional opinions of the authors as of the time of writing (2021). The fundamental purpose and content are similar to previous versions (2004, 2012) of this document. Earlier versions, including translations of the original version into French, Spanish, German, Japanese, Chinese, and Turkish, are available at https://icord.org/research/iccp-clinical-trials-information/. 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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Appendix A

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
1. Safety			
a. Are there safety risks associated with this experimental treatment?			
b. Could my condition or my health get worse after this experimental treatment?			
c. If so, can you describe the possible risks associated with this experimental treatment?			
2. Possible benefits			
a. Can you describe the possible specific benefits of this experimental treatment?			
b. Can you describe the maximum level of recovery I might see after this treatment?			
c. Can you describe how any potential benefit will be measured?			
3. Clinical trial protocol			
a. Is this study being conducted under the oversight of an appropriate qualified regulatory body?			
b. Can you describe what clinical trial phase this particular trial 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
4. Payments and costs			
a. Do I have to pay for the experimental 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)?			
5. Participation in other trials			
a. Will my participation in this 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?			
6. Preclinical or prior clinical evidence			
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 specialists that disagree with the validity of this trial? What are their objections?			
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?			

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: YES; no one can guarantee total safety, but some information should be available about possible risks based on either animal data or earlier phase clinical trials.
b. *Could my condition or my health get worse after this experimental treatment?*
   Answer: YES; if someone tells you there are 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 willing to discuss in detail the possible risks.

2. Possible benefits

a. *Can you describe the possible specific benefits of this experimental treatment?*
   Answer: The investigator should give you a range of possible benefits, from very subtle to more noticeable functional changes you might or might not experience.
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.
c. *Can you describe how any potential benefit will be measured?*
   Answer: The investigator should be able to describe all the different kinds of tests you will undergo to evaluate your progress after treatment.

3. Clinical trial protocol

a. *Is this study being conducted under the oversight of an appropriate qualified regulatory body?*
   Answer: YES; the investigator should be able to provide you the details immediately. Be concerned if the answer is vague or consists of excuses why not.
b. *Can you describe what clinical trial phase this particular trial falls within (Phase 1, 2, or 3), and what is the emphasis of study for this phase of the trial program?*
   Answer: The answer should be immediate, understandable, and in as much detail as you want.
c. *Is there a control group in this study?*
   Answer: YES, especially for drug and cell therapy trials. If not, is this a Phase 1 open-label study (safety only)? If not, then you should be wary. However, in a rehabilitation study involving people who have lived with a SCI for many months or years, the focus may be on changes from a baseline for the individual established during the trial, and a separate control group might not be included.
d. *Could I be randomly assigned to the control group?*
   Answer: YES for Phase 2 and 3 trials. If not, then this is likely not a scientifically strong clinical trial.
e. *Can you tell me how long I will be assessed for any change in outcome?*
   Answer: This could vary widely, from days or weeks to as much as a year or more, depending on the treatment and its expected effect on your recovery and safety. It is possible that you may have to commit the most time during 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 physically and ethically possible in Phase 2 and 3 trials, the answer should be YES. If not, it could be an open-label Phase 1 trial or a rehabilitation or surgical trial where blinding is not possible or safe. In other cases, you should be wary. Sometimes you cannot help but know what group you are in, but the investigators should ask you not to tell the examiners which group you are in until the trial is over and all of the data are analyzed.

g. Will the investigators and examiners be blind to what treatment I have received?
Answer: This should be a definite YES, for trial staff who can refrain from knowing the treatment being administered. If not, it may not be well-designed trial to determine the therapy's effectiveness without bias, and you should be suspicious.

4. Payments and costs

a. Do I have to pay for the experimental treatment?
Answer: This should be NO. If Yes, then this is not a clinical trial you can trust. You should be suspicious and 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 healthcare insurance provider, may have to pay for the current standard of medical care. You should be informed about whether the trial sponsor will pay for treatment of any complications you might experience because of your participation in the trial.

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

5. Participation in other trials

a. Will my participation in this trial limit my participation in other SCI clinical trials?
Answer: This could be a possibility unless the potential effect of the treatment being tested is known to be temporary. 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 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 and compare.

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?
Answer: This is a possibility, unless your SCI condition changed, or there was a limited time for treatment after SCI that will have passed. 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 describe the previous evidence in terms you can understand, including the strengths and limitations of the treatment approach. Evidence may come from animal studies or a related human disorder. Remember that effects in animals, such as recovery of walking, cannot be expected to translate directly to effects in human beings.

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, confirming the potential benefit when investigating this therapeutic target or treatment approach.

c. Are there specialists that disagree with the validity of this trial? What are their objections?
Answer: The answer here may be YES, as there are almost always some difference in 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

compared to any alternatives, 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. 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 B). In any case, you should discuss your concerns and aspirations with your healthcare 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?

Answer: The answer should be YES, and you should be able to verify the credibility of the study and the credentials of the investigators via other sources or independent websites.

Appendix B

Experimental Treatments for SCI – Summary

Note: This section summarizes the most important aspects of the document. However, we **strongly** recommend that you read the entire document to fully understand it. Reading this section alone will not provide you with the necessary knowledge to make an informed decision that could have consequences on your well-being.

What is the difference between a clinical trial and clinics offering unproven procedures?

Clinical trials are well-designed, objective tests of experimental treatments. They are regulated by local and governmental authorities and follow a defined scientific process to protect you from possible harm and to discover if the therapy is beneficial. Clinics offering unproven medical procedures do not follow these rules and cannot provide objective evidence the treatments they sell will work and not cause harm.

How do I tell whether an experimental treatment is part of a valid clinical trial program?

The article will explain the trial process and guide you on how to get more information. For a start, you should not be asked to pay for the experimental treatment being tested in a regulated, scientific trial. You may incur some expenses, such as insurance copay fees, deductibles, or accessory costs (e.g., travel), but the cost for the treatment being tested is covered by the trial sponsors.

Why are clinical trials necessary?

Clinical trials are designed to provide clear evidence that a treatment is safe and beneficial. Every experimental therapy and trial poses some risk of causing unintended complications. Well-designed clinical trials document both benefits and unforeseen risks and are structured to determine if any benefit is due to the treatment rather than other factors, such as natural recovery or additional rehabilitation used along with the experimental treatment.

What makes a good clinical trial?

This depends on the trial phase (as explained in this section of the article). To test if a treatment is effective, a properly designed clinical trial follows a strict, scientifically accepted process that generally compares a group that receives the experimental treatment to a control group that gets an inactive (placebo) treatment. Other aspects of the trial should be as similar as possible for both groups. To remove bias or conflict of interest, trial assessors and participants may not be allowed to know which treatment has been delivered (this is called "blinding").

How are clinical trials structured?

Each phase of well-designed clinical trials is governed by local, regional, and/or federal agencies that review the evidence. They ensure that the requirements of each phase of the process have been followed, and that participants have not been harmed by the experimental treatment, before allowing the next phase to proceed.

What if I get assigned to the control group?

Trials are conducted because we do not yet know if an experimental treatment is beneficial or potentially harmful. Comparisons, such as between people who get a treatment or do not, help avoid bias so that impartial conclusions can be made. Volunteers participating in a trial, whether they are in the experimental or control group, should always receive the current best care available. Many trials will eventually offer the treatment to the control group if it is determined that the benefit to them, based on the current status of their injury, outweighs the risks.

What are the various trial phases?

Clinical trial phases are defined by regulatory authorities for testing, and ultimate approval, of new drugs, cellular therapies, and devices. Testing usually requires a series of trials in sequential phases (Phase 1, 2, and 3) with results that indicate both safety and meaningful benefit before a regulatory

agency will consider approving an experimental treatment for use in regular care. Unfortunately, it is quite common to see an experimental treatment fail, even when early signs showed great potential. Short-cutting these processes will likely result in a failure.

What are regulatory oversight and registration of clinical trials?

National authorities regulate trials testing new drugs, cellular therapies, tissue transplants, devices, or technologies. Trials that test surgical procedures or rehabilitation activities may not be regulated by those agencies. However, all genuine trials should have approval from the local human research ethics committee. Treatments are approved for specific disorders, or segments of the population, so off-label use is still a form of unproven therapy. An increasingly common practice is the registration of trials on a central, public website, which is not a substitute for regulatory approval. The trial investigator will be able to inform potential participants about the registration details and agency approval associated with the trial.

What is required for participation in a clinical trial?

A well-designed trial, especially in the early phases, needs to limit testing to a group of participants who are similar to each other in order to have the best chance to show a benefit. Therefore, a person interested in participation must match a set of criteria (called inclusion and exclusion criteria) that is determined before the trial is allowed to proceed.

What is informed consent?

Before you participate in any trial activities, all aspects of the trial must be explained to you, including what is being tested and how, what is expected of you, and all potential risks and benefits, both short- and long-term. This occurs via a thorough discussion with the investigator during which you may ask any and as many questions as you wish. Only when you feel all your questions have been answered to your satisfaction will you be asked to sign the form that says you have been informed and give consent to participate.

What if I have already received an experimental therapy?

Having already received an experimental therapy may or may not disqualify you from receiving another experimental therapy. This depends on what the previous experimental therapy was and how it might interact with the next experimental treatment. This can only be determined on a case-by-case basis, in discussion with the investigator of the trial that you are considering.

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

You will become a volunteer participant (e.g., be enrolled) once you have given your informed consent. After that, the length of time you participate depends on the trial but typically involves several hours (during each of several visits) over several weeks, months, or even longer. You are free to withdraw your consent and stop participating at any time and for any reason.

What treatments are available now?

Surgical procedures, rehabilitation, drug therapies, and assistive technologies, including some types of electrical stimulation, are currently used in standard care. Surgical decompression and stabilization of the bones of the spinal column very soon after spinal injury are accepted best practices in many places around the world. Surgery is also indicated to treat complications including cysts expanding within the spinal cord (syringomyelia) that can cause loss of sensation or motor function, pain, and autonomic disturbances in 5% to 10% of people with chronic SCI. Many forms of rehabilitative strategies administered by trained therapists are standard practice, some including assistive technologies or functional electrical stimulation to maximize functional recovery. SCIRE (www.scireproject.com) provides information about accepted rehabilitation strategies as well as drugs currently approved to treat spasticity, pain, metabolic functions, and management of bladder, bowel, respiration, cardiovascular, sexual, reproductive activity, bone health, community mobility, and quality of life.

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

Current potential therapeutic interventions (e.g., new drugs, cell transplants, rehabilitation strategies, or assistive devices) are focused on neuroprotection, repair/regeneration, neuroplasticity, and replacement/assistance of function. More details can be found at SCITrialsFinder.net.

Should I *still* consider receiving an unproven treatment outside of a clinical trial?

This is a personal choice, and the information provided here will help you to decide. If you choose to receive an inadequately tested treatment at a clinic claiming success, you may pay for a treatment that will most likely bring you no improvement and possibly cause adverse effects. You may need to undergo extensive travel with its attendant risks. Complications may create new health problems, and there is a chance of losing further functions, causing pain, or even life-threatening problems. You should discuss these with your healthcare provider(s) before making a final decision.

What if I read about it in the media?

Regulatory agencies strictly control marketing of experimental treatment trials; however, clinics that sell unproven treatments often advertise directly to patients through clinic websites, brochures, and social media platforms. Positive results from trials of experimental treatments are published in peer-reviewed journals while clinics selling unproven treatments mainly provide selected testimonials, questionable data, and lack oversight by regulatory agencies.

Where can I get good advice?

Good advice is available through your medical professionals, nonprofit organizations (professional societies, government and nongovernmental organizations, foundations, academic or medical research centers, and advocacy groups), as well as published clinical and scientific literature in reputable medical journals.

Appendix A: What to ask before taking part in a clinical trial or human study?

A participation checklist, with questions that you can ask during the informed consent process, is available in Appendix A, along with information to help you understand the answers you might receive.

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.

Activities of daily living (ADL): activities involved in self-care, bowel and bladder 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

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.

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 nonfunctional. 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

Bias: Consciously or unconsciously, the desire to find a therapy beneficial can prejudice the interpretation of trial outcomes. This will lead to conclusions that do not reflect the true benefit or harms caused by a treatment, or ignore the impact of other factors. Bias in the design, conduct, analysis, and interpretation of a clinical trial can falsely increase the perceived benefits while overlooking risks.

Blinded assessments: those evaluations conducted on a clinical trial subject where the evaluator does not know 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: either the clinical investigator or the subject, but not both, are blinded.

Double blind: 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. 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.

Clinical Trial: a human research program that will 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. 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 provides a clinically meaningful benefit, to further explore safety and perhaps dosing.

Phase 3 is the pivotal trial phase to test the effectiveness and safety of the therapy and involves the largest number of participants, usually 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.

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. 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.

Electrophysiological testing: the process of examining the effects of electrical, magnetic, or natural stimulation. Electrophysiological testing can be very informative for examining nervous system function, particularly the connectivity across the damaged spinal cord.

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/improvement: 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.

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 grading of sensory responses to touch and pin prick at each of 28 areas along each side of the body and a grading of the strength of contraction within 10 representative (key) muscles.

Motor score: based on the ISNCSCI assessment of muscle strength. The motor score is calculated by assigning to the muscle group a score between 0 (no detectable contraction) and 5 (active contraction against resistance considered to be normal with a full range of movement). 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 set of the ASIA motor score for the leg and foot muscles. The Upper Extremity Motor Score (UEMS) is a maximal 50-point set of the ASIA motor score for the arm and hand muscles.

Motor Level: defined as the most caudal (lowest) spinal level having a muscle strength of 3/5 or greater while all key muscles above are normal (5/5).

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 for both sensory and motor functions. Thus, up to four different segments may be identified in determining the motor and sensory level. Note:

The level of spinal column (bone) injury may not correlate with the neurological level of spinal cord injury.

Open label: both the researcher and the trial participant know the treatment that the participant is receiving.

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.

Peer review: a process by which experts in the same field (peers) evaluate the results of a study or trial. This ensures both quality and validity.

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 or examination of 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. 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 reflects the expectations of the participant and/or the investigators providing the treatment (also see bias). A placebo drug or "sham" surgery can remove this issue.

Plasticity: refers to changes that occur in the organization of the brain and spine. Neuroplasticity can be either positive (functional recovery) or negative (autonomic dysreflexia or neuropathic pain). Experiments have demonstrated that active rehabilitation programs improve neuroplasticity with the physical and occupational training. A common and surprising consequence of 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. The main thing is the adult brain and spine are not "hard-wired" with fixed and immutable structure. There is evidence that formation of new nerve cells occurs in the adult human brain and spinal cord.

Quadriplegia: see Tetraplegia

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 affect trial outcomes. For this reason, they provide the best evidence of efficacy and safety.

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 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 of 0 (absent sensation), 1 (impaired or abnormal sensation), or 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 pin prick.

Sensory level: is defined as the spinal segment corresponding with the most caudal area having a normal score of 2/2 for both pin prick and light touch.

Spinal Cord Independence Measure: (or SCIM) a scale for assessing function and activities of daily life that appears to be better than the Functional Independence Measure (FIM) for assessing SCI. 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 & sphincter management* (breathing, bladder, bowel, use of toilet) max. = 40 points.
3. *Mobility* (in bed, transfers, indoors and outdoors, wheelchair, walking) max. = 40 points.

Spinal decompression: a surgery to relieve pressure on the spinal cord (or nearby nerves) to prevent further tissue damage and other structural complications.

Sham operation/procedure: a surgical procedure in which the subject is operated on but does not receive the experimental intervention. Like a drug placebo treatment, this is done to keep trial assessors from knowing who received the treatment, so the surgery may be only superficial to give an appearance that the intervention was given.

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).

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 References

Note: These publications are primarily directed to a clinical and scientific audience.

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