What you need to know about stem cell therapies
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While media reports about the potential of stem cell therapies are common, much of the research is still in the earliest stages, involving basic laboratory work and animal studies, and some research has been started with patients. Most stem cell therapies are still considered research and are a long way from the clinic. Indeed, stem cell and other treatments must be tested in animals and then on humans and shown to be safe and effective before they can be made generally available to patients. Nevertheless, many clinics around the world are offering, usually via the internet, so-called stem cell treatments. These “therapies” — which are more properly called “interventions” because of their questionable therapeutic value — are scientifically unproven and have not received regulatory or ethics approval. Some have been shown to harm patients.

In many cases, patients travel to a range of countries to receive unproven stem cell interventions. For this reason it has also been called “stem cell tourism.”

While scientists, ethicists and medical professionals generally advise against unproven stem cell interventions, the reasons for this are not always clear and may seem to be contrary to the needs of patients. You may, for example, wish to know why it takes so long to approve new stem cell interventions or why it is wrong to pay for an unproven intervention that might help your condition.

This booklet is designed to answer these and other questions so that you can make more informed decisions about your health. The booklet has been reviewed by patients, members of the public, and academic experts to ensure it adequately captures a range of perspectives. This booklet has three parts:

1. Stem Cells and Stem Cell Interventions
2. How Does Stem Cell Research Move from the Lab to the Clinic?
3. What You Need To Know About Unproven Stem Cell Interventions
The human body contains hundreds of different types of specialized cells such as those that make up muscle, fat, the nervous system, and skin. All of these specialized cells trace their origins back to stem cells. Stem cells can give rise to different types of cells through a process called differentiation. If scientists can turn stem cells into specific cells, they might be able to treat different diseases and injuries by transplanting them into patients — this is a form of regenerative medicine (see Figure 1). For example, if heart muscle is damaged after a heart attack, stem cells might be used to make new heart muscle to be transplanted into the heart to repair it. There are many types of stem cells and they all have unique biological properties (see Box 1).

**Figure 1. Stem cells and regenerative medicine**

Stem cells can differentiate into many cell types. Specific cells derived from stem cells can be transplanted into a patient to treat a disease or injury, such as Parkinson’s disease, spinal cord injury, Alzheimer’s disease, heart disease, diabetes, and others.

**Stem cell interventions**

Stem cell interventions are used to describe many different types of treatments that use stem cells or cells that come from stem cells. The goal is to use these cells in order to replace tissue that was damaged from injury or disease. However as simple as this may sound, there are major obstacles to the successful use of these kinds of interventions, including the fact that the patient’s body may reject transplanted cells. As with organ transplantation, this generally requires patients to also take drugs that suppress their immune system. For this reason, scientists are excited about induced pluripotent stem cells because they can be created from the cells of the actual patient and, as a result, they may not be rejected after transplantation. Similarly, mesenchymal stem cells might also restrain the immune system and escape rejection (see Box 1).

Stem cells can be transplanted in different ways, for example, through a surgical operation or through injection into the blood stream. The different transplantation procedures carry risks, including bleeding, infection, or tissue damage. In addition, the transplanted stem cells pose risks. They may form tumors or migrate away from the area they were transplanted to another place in the body and cause unknown side effects.
Scientists are performing experiments with different stem cells and trying many ways to treat diseases. There are some examples of this at the end of Part 2. For more information on the biology of stem cells, please see the following references:


### Stem cells and their properties

<table>
<thead>
<tr>
<th>Stem cell type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embryonic stem cells</td>
<td>These are pluripotent cells, which mean they can give rise to all cell types of the human body. They are obtained from very early-stage human embryos.</td>
</tr>
<tr>
<td>Induced pluripotent stem cells</td>
<td>Like embryonic stem cells, these cells are also pluripotent and, in theory, give rise to all cell types of the human body. These cells are made by taking adult cells (e.g., skin cells) and using specific genes that change the cells making them pluripotent.</td>
</tr>
<tr>
<td>Adult stem cells</td>
<td>These cells are found in different tissues in the body. Adult stem cells are limited in their ability to turn (differentiate) into various types of cells. For example, hematopoietic stem cells are a type of adult stem cell and they can become all the cells of the blood and immune system i.e., red blood cells, T-cells, etc.</td>
</tr>
<tr>
<td>Mesenchymal stem cells</td>
<td>This type of adult stem cell has some unique properties that might be good for regenerative medicine. Mesenchymal stem cells are found in bone marrow, fat, umbilical cord blood, circulating blood, and the placenta. Many stem cells, including mesenchymal stem cells, can migrate within the body to areas of damage. This is useful because you want the cells to go to the injured or damaged area in order to replace what was there. Mesenchymal stem cells might not trigger an immune reaction after they are transplanted and this may mean they will not be rejected by the body. Mesenchymal stem cells also produce many molecules (e.g., growth factors) that are released and help surrounding cells grow and regenerate.</td>
</tr>
</tbody>
</table>
Before scientific knowledge can become an effective treatment, it must go through a process called **clinical translation**.

This process has several well-defined steps that are designed to help ensure safety and effectiveness. The clinical translation process starts from preclinical research moving to clinical research until the product becomes approved (see Figure 2).

**Preclinical research**

The first stage in the clinical translation process is known as preclinical research and may also be called laboratory, animal, or bench research. Preclinical research occurs in a laboratory. The goal is to show proof-of-principle that the intervention has the potential to be safe and effective for further testing. In this stage of research, scientists perform experiments with stem cells in animals that mimic a disease or injury similar to humans. Scientists need to make sense of the disease, assess the problems, and figure out how to fix it. The research must be reviewed by other independent scientists — a process known as peer review — to ensure it has been done well. The work is then published so that other scientists can repeat the experiments and verify the results. When there is sufficient evidence of safety and efficacy (effectiveness), the research can move into clinical phases involving human participants.

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**Figure 2. Clinical translation process**

<table>
<thead>
<tr>
<th>Preclinical Research</th>
<th>Quality Control</th>
<th>Clinical Research</th>
</tr>
</thead>
</table>
| Laboratory and Animal Research | - Assess cell function  
- Make sure cells are free of contamination  
- No animal products  
- Scale-up to produce sufficient quantities | Phase I-III  
Test safety and/or effectiveness | Market Approval / Phase IV |
The need to receive ethics approval for clinical research

Prior to beginning any clinical research involving humans, the research must receive ethics approval to ensure human participants are adequately protected. Ethics review usually occurs at the location where the clinical study is going to take place — such as a hospital, clinic, or research center. An independent group of experts in science, clinical research, ethics, law, and public/patient representatives, none of whom are connected with the research being proposed, will review the ethical aspects of the research project. These groups are called by different names such as Research Ethics Boards, Institutional Review Boards, or Research Ethics Committees, among others. These boards/committees evaluate, among other things:

• the research protocol (i.e., what the researchers plan to do);
• how and what information is provided to participants;
• how consent will be obtained;
• whether the potential benefits of the research outweigh the risks;
• how the participants will be monitored; and
• that participants are able to withdraw from the study for any reason.

Once these boards/committees approve the study, the scientists can begin to recruit volunteers. The clinical study team should, as part of the consent process, provide potential participants with a consent document that will explain all of the information outlined above.

Medical innovation

There are also types of studies that fall outside the usual clinical trial framework. Medical innovation is when a doctor treats a small number of very ill patients because there is a scientific reason to do so based on preclinical studies showing safety and efficacy, and the doctor thinks it might benefit his/her patients. Medical innovation is not considered “research.” It is an approach to treatment. And because it is only done on a small number of patients, scientists would need to follow-up with full-fledged clinical trials to ensure safety and efficacy before it could be marketed.
Clinical research

Research that tests an intervention in humans is called clinical research. Clinical research can begin after scientists have sufficiently demonstrated safety and effectiveness of a potential treatment during preclinical research. The evidence from all the preclinical experiments is evaluated by regulatory agencies. Regulatory agencies are found in many countries, such as the U.S. Food and Drug Administration, Health Canada, and the European Medicines Agency. Regulatory agencies are concerned with the safety of participants and the effectiveness of the intervention. Regulators examine several things, including:

- the clinical protocol;
- quality of previously collected laboratory data;
- how the participants will be monitored;
- whether ethics approval has or will be obtained;
- where the research is going to take place;
- the risks to participants; and
- the potential benefits of the research.

It is generally the responsibility of the scientists or organization sponsoring the trial (e.g., a company) to cover all costs associated with conducting the research. Be very cautious of any clinical trial that requires payment from research participants.

There are a number of different types of clinical trials, from the earliest phase 1 trials that are designed only to see if the intervention is safe, to final phase 3 and 4 trials that show whether the treatment is effective (see Box 2 and Figure 2).
Clinical trials are research, not therapy

The goal of clinical trials is to gain knowledge. In some cases patients may benefit, but clinical trials are not intended as a way to provide therapy. In fact, for some types of clinical trials, there is no guarantee that a person will receive the experimental treatment as they may be randomly placed in a placebo group (a group that receives a mock treatment to control for the power the mind can have in making us feel better if we think we are getting treatment).

For more information on clinical trials and clinical translation, please see the following references:

Stem cell clinical trials and treatments

While stem cells may one day treat many diseases, to date there are only a handful of legitimately tested therapies. These include the use of blood-forming (hematopoietic) stem cells as part of treatments for some cancers and other diseases of the blood and immune systems. Commonly known as bone marrow and blood cell transplantation, these treatments have been done for a long time with good success and are well developed. However, most stem cell research is still at the laboratory stage, or in early clinical trials.

Most of the ongoing clinical trials for stem cell therapies are in phases 1 and 2. The majority are using adult stem cells — primarily blood (hematopoietic) stem cells — and some are using stem cells from the umbilical cord. These cells are being used to treat cancers and graft versus host disease. Graft versus host disease is a complication that occurs after bone marrow or blood stem cell transplantation. Clinical trials are investigating the use of mesenchymal stem cells to treat graft versus host disease, and to study heart attacks, liver problems, multiple sclerosis, and other diseases. Clinical trials are also being done for neurological conditions, cardiovascular diseases, eye conditions, and diabetes. There are only a few phase 1 trials using human embryonic stem cells to study spinal cord injury and eye disorders. The Japanese government has recently approved the first pilot study using cells created from induced pluripotent stem cells to study age-related macular degeneration (causes loss of vision). Your doctor should be able to help guide you to which types of clinical trials you may be eligible for.

For more information on stem cell clinical trials, please see the following references:

Clinics around the world advertise stem cells as legitimate therapies, alternative medicine, or experimental treatments for a wide variety of different diseases and conditions. Most of the interventions being offered have not been properly tested and there is little or no solid evidence to suggest they work or are safe. Clinics that offer unproven stem cell interventions are usually found in countries with less regulation and oversight over medical products, research and treatment, but more of these clinics are starting to open in highly regulated countries like the U.S. Below, you will find the answers to common questions about unproven stem cell interventions.

### What types of stem cells are used and what diseases are treated by stem cell clinics that provide unproven interventions?

Much of what is known about unproven stem cell interventions comes from studies examining what services the clinics advertise (see Box 3).

<table>
<thead>
<tr>
<th>Stem Cell Types</th>
<th>Where the Stem Cell Comes From</th>
<th>Transplantation Procedures</th>
<th>Interventions Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult stem cells</td>
<td>Patient</td>
<td>Surgery</td>
<td>Multiple Sclerosis</td>
</tr>
<tr>
<td>Embryonic stem cells</td>
<td>Other adults</td>
<td>Orally (swallowing)</td>
<td>Diabetes</td>
</tr>
<tr>
<td>Fetals stem cells</td>
<td>Cord blood</td>
<td>Topically (placed on skin)</td>
<td>Spinal Cord Injury</td>
</tr>
<tr>
<td></td>
<td>Fetuses</td>
<td>Injecting into blood, skin and muscles</td>
<td>Autism</td>
</tr>
</tbody>
</table>

- Parkinson’s disease
- Cerebral Palsy
- Blindness
- Hair loss
- Sports injuries & back pain
- Anti-aging
Where are stem cell clinics that provide unproven interventions found?

Stem cell clinics that provide unproven stem cell interventions are found around the world. Traveling to another country for a stem cell intervention is called “stem cell tourism”. Some clinics have been shut down by government officials in one country (e.g., the largest XCell clinic in Germany was closed), but have reopened in another location (sometimes using a different name). Clinics providing unproven stem cell interventions have been reported in China, Mexico, India, Panama, Ukraine, Russia, Costa Rica, Dominican Republic, Thailand, Philippines, and the U.S., among other places.

How do you spot a clinic providing unproven stem cell interventions and what questions should we ask them?

Stem cell clinics offering unproven interventions generally have the following characteristics:

Skewed Advertising
Many stem cell clinics advertise their interventions as alternative or experimental treatments. This does not mean they are unable to provide evidence of safety and effectiveness of the intervention. Alternative therapies can also undergo regulatory approval. You should ask the clinic for scientific evidence of effectiveness of alternative stem cell therapies. Your doctor can help you better understand and evaluate the scientific evidence, such as scientific publications. If clinics claim that the stem cell intervention is experimental, then it could mean it is a clinical trial.

Clinical trials should:
- be registered and have a clinical trial registration number;
- have strict criteria for who can enroll;
- have obtained ethics and regulatory approval; and
- be provided at no cost to participants who enroll in it.

Clinics offering unproven stem cell interventions often focus on the emotional and humanitarian aspects of how the intervention helps people. They tend to overemphasize benefits and underplay the risks. Every medical treatment has some risks and all known risks should be explained. Prior to starting a clinical trial, the doctors must provide you with information including:

- how the study is designed;
- the procedure to be used;
- the risks and benefits; and
- the alternative choices you have other than participating in the trial.

If this information is not freely provided, then you should be cautious of whether the intervention being offered is a legitimate clinical study.
Patient testimonials
Stem cell clinics providing unproven interventions often claim to 'prove' their intervention is effective by relying on the testimonials of other patients. Patients are hoping that a treatment can help them and they believe it does. After an intervention, patients might feel they have benefited. But this might not be long lasting and may not be due to the intervention. Scientists use many ways to assess whether an intervention is effective. They can ask patients about their level of comfort or their ability to regain a function, e.g., better movement. However, they also use special devices, blood tests, biopsies, imaging scans and other tests that do not depend on the patient’s self-reports. If a clinic claims effectiveness based only on quotes from other patients, it is a good idea to ask for more evidence (e.g., scientific publications). Your doctor can help you better understand the scientific publications.

Sometimes if you ask a clinic for scientific publications, they may say their research is not published because they are patenting the intervention. This might not be true. Once a patent is filed, the idea is protected and scientists freely publish their results as they need other scientists to see if they can reproduce their findings. So there should be no reason why scientific evidence in the form of publications cannot be provided.

One Size Fits All Treatment
Many stem cell clinics offering unproven interventions also:

- use one type of stem cell;
- use one type of transplantation procedure (e.g., injection into bloodstream); and
- claim that it can treat a range of very different diseases and injuries because stem cells move to the injured or damaged area.

Diseases are very specific and a one-size-fits-all method of treatment is not likely to work. Treating diseases effectively with stem cells will require using a specific cell type and a specific transplantation procedure.
Cost and repeated application
Reports have shown that stem cell clinics providing unproven interventions charge from $5,000 to $30,000 (or more). In addition, many clinics ask for repeated treatments which cost more money. Of course, patients can spend their money however they wish. Although there may be associated travel costs and other expenses, clinical trials do not require patients to pay for the intervention. Because there are risks with any clinical procedure, you need to also consider what will happen if something goes wrong and you need emergency or additional care. Will your health insurance in your home country cover these costs? Will the clinic providing you the interventions cover these costs? Where and how will you receive any follow-up care that you might need? You can ask these sorts of questions when you are considering a stem cell intervention.

Why does it take so long to make stem cell therapies?
There are several reasons why it takes so long to make a stem cell therapy. Science is a long process because scientists need to understand what is wrong when someone has a disease and how to fix it. As the human body is complex, lots of experiments are done and many do not work. When scientists find promising results, they have to work out the right conditions. As research moves from the laboratory using animals to human research, sometimes what works in animals may not work in humans. Even after scientists discover a way to treat a disease in animals, they have to make sure the stem cells they are putting inside people are safe and will not form tumors or create other negative side effects. Scientists need to make sure the stem cells don’t have any contaminants (e.g., bacteria, viruses or fungus) and that stem cells behave as expected. This includes cells taken from and transplanted back into the same patient because the cells can become contaminated even in sterile surgical rooms.

The entire clinical translation process can take 15 or more years. Making sure stem cell interventions are safe and effective is difficult as they are new types of medicine. Regulatory authorities around the world are working to make the process more streamlined and efficient.
What are the risks of receiving unproven stem cell interventions?

Many patients who seek stem cell interventions say they have nothing to lose even if the treatment is unproven. However, these unproven stem cell interventions can be dangerous. Some patients who have received unproven stem cell interventions have developed lesions, tumors, cancer, tremors and some have died. These sorts of complications may wind up being more painful, make the condition worse, and could shorten lifespan. Because the unproven interventions by stem cell clinics cost quite a bit of money, including travel and accommodation, there are important financial concerns as well. If the clinic doesn’t treat side effects, after returning back home, you may have to pay for additional treatment. The additional treatment may or may not be covered by insurance companies or the health care system. Lastly, because legitimate clinical trials are very specific about which patients are eligible to be in the study, receiving an unproven stem cell intervention may disqualify you from enrolling in future legitimate research trials.

Are stem cells taken from your own body safe?

In some cases, stem cells can be taken from your own body and later transplanted back. This is known as autologous stem cell transplantation. In other cases, stem cells are taken from other people and transplanted into your body, which is called allogeneic stem cell transplantation. When cells from other people are put into your body, your body may have an immune reaction to the cells because they are foreign (not from your body). Although it is less likely that you will have an immune reaction with cells taken from your own body (autologous transplantation), this doesn’t make the procedure safe. For example, the stem cells themselves can be contaminated or form a tumor. The transplantation procedure (e.g., surgery) and other drugs used (e.g., anesthesia) also have risks.

Do scientists, doctors, and regulators have a vested interest in maintaining the status quo?

Several people have suggested that physicians, scientists and regulators have vested interests in keeping stem cell research going and not providing treatments to patients who need them. This is something you may hear from clinics offering unproven stem cell interventions. Some have gone so far as to say that there may even be a conspiracy to keep medicines from patients.

This argument is flawed. Health care is one of the most expensive budget areas for governments and so the healthier a population, the better. As well, research (including clinical trials in particular) is incredibly expensive. Drug companies invest millions of dollars into research and development and only see a profit when they can sell a therapy. Likewise, scientists and physicians generally receive the greatest benefit (financial, professional reputation, personal satisfaction, etc.) when they develop interventions that help people — indeed, given the prevalence of certain diseases, some of these people are likely to be friends or members of their own family. In addition, almost all scientists, doctors, and regulators are genuinely concerned for patient welfare. They want to make sure that patients are receiving something that is not going to cause further problems and will hopefully benefit them.
There is no question that only those struggling with disease or debilitating conditions can truly understand what they and their families are going through, and frustration with what may seem like regulatory hurdles is very understandable. Efforts are on-going to improve and streamline the regulatory process to facilitate more efficient translation of stem cell research into safe and effective therapies.

I have heard of stem cells derived from fat that can help with treating injuries and all sorts of diseases. Are these valid therapies?

Several prominent people including politicians, celebrities, and athletes have received stem cell interventions taken from their fat or other parts of their body. Mesenchymal stem cells are found in fat and they do have the clinical potential to treat many diseases and injuries (see Box 1). Although several mesenchymal stem cell clinical trials are ongoing, many are in early phases. Because mesenchymal stem cells can be removed from fat and put back in your body, some people feel this approach does not require regulatory approval. However, before being reintroduced to the body, these cells are grown in a laboratory to make many more cells. As such, some regulators, such as the U.S. Food and Drug Administration, believe these interventions do require regulatory approval because they may have side effects and we cannot know if they are truly effective until they are properly tested.

For more information on unproven stem cell interventions, please see the following references:

- MS Society UK and others. 2010. “Stem Cell Therapies in MS” http://www.mssociety.org.uk/ms-resources/stem-cell-therapies

We cannot know if mesenchymal stem cell-based interventions are truly safe or effective until they are properly tested.
What you need to know about stem cell therapies

Summary points

This booklet is a starting point to help you distinguish between legitimate research or therapy and unproven stem cell interventions. It includes other good sources of information to help you get as informed as possible before you make such an important decision about your health.

Stem cell research has the potential to treat many different diseases and injuries, but most stem cell research is still at the laboratory stage or in early clinical trials.

Developing stem cell medicines is a long road because the clinical translation process is complicated, but essential to make sure stem cell interventions are safe and effective.

There are clinics around the world offering stem cell interventions that have not been proven to be safe or effective. These interventions are potentially risky and often expensive.

When considering a stem cell intervention, there are some important questions to consider to make sure you know what you are getting yourself into and that you understand the risks.

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