Substantial progress in stem cell research has been made since the first report on the derivation of human embryonic stem (ES) cells. As we celebrate the 10th anniversary of this landmark event, we also witness new scientific and policy milestones that reinvigorate hopes for moving forward the clinical translation of stem cell-based interventions. Nevertheless, stem cell-based therapies remain largely at the experimental stages and the road towards the clinical is still paved with major scientific and ethical hurdles. A positive signpost though, is the recent approval of what will be the world’s first clinical trial of a hESC-derived product by the United States Food and Drug Administration (FDA). Geron Corporation has been granted clearance for an Investigational New Drug (IND) application for the clinical trial of GRNOPC1 in patients with acute spinal cord injury.

This article briefly addresses the rationale for establishing clinical trial registries (CTR) and the challenges arising from their implementation. A Clinical Trial Registry (CTR) is a publicly available database of all human interventional clinical trials regardless of the stage of development – at inception, while in progress or after completion – and of their publication status. The raison d’être for mandating the prospective registration of all stem-cell based clinical trials will be discussed. It is beyond the scope of this paper to provide a comprehensive analysis of the wide range of possible approaches, policy responses and their implications. However, we want to provide a starting point for discussion surrounding key questions and challenges facing clinical trial registration, questions that go beyond a call for voluntary publication.

Moving Towards the Clinic: Science, Policy and Ethics

Alongside these new scientific advances, important policy developments have also taken place. The International Society for Stem Cell Research (ISSCR) adopted the first professional guidelines setting standards for the clinical translation of stem cells in three major areas: cell processing and manufacturing, pre-clinical studies and clinical research. The guidelines encompass recommendations and establish principles for the scientific, clinical and ethical conduct of translational stem cell researchers, clinician-scientists, and regulators in the international community.

In the context of medical research ethics in general, another significant policy development took place while we celebrate a decade since James Thomson’s discovery. The World Medical Association amended the Helsinki Declaration, “the primary source and arbiter of research ethics worldwide.” While the Declaration is addressed primarily to physicians, the WMA intends for the Declaration’s scope to reach a full range of stakeholders.

Both the Helsinki Declaration and the ISSCR guidelines recognize that authors, editors and publishers have ethical obligations with regard to the full publication of research results, whether negative, inconclusive or positive. Similarly, they recognize the right of research participants in particular and society in general to have access to this information. Moreover, the Declaration of Helsinki took the unprecedented move to call for the registration of every clinical trial in a publicly accessible database before the recruitment of the first research subject (Principle 19). In contrast, the ISSCR guidelines called only for the publication of “both positive and negative results and adverse events” at “professional scientific conferences or in peer-review scientific journals before reporting their research to the lay media or to patient advocacy groups and associations” (Recommendation 33).

The aforementioned policy recommendations are of significant importance as they establish principles for strengthening transparency in clinical research by calling for the prospective publication of research results. By promoting transparency, they are encouraging scientific and ethical integrity in clinical trials. They are also seeking...
to maintain public trust, essential for the feasibility of any scientific endeavor but even more so in an area that has elucidated so much political, social and ethical controversy, that of stem cell research.

Over the past decades, clinical trials of stem cell-based interventions (e.g. transplantation) have been carried out using umbilical cord blood stem cells and autologous adult stem cells (e.g. hematopoietic stem cells or blood stem cells) to treat diseases such as leukemia, lymphoma and several inherited blood disorders. The safety and efficacy of these interventions has been well established. Conversely, interventions using human embryonic stem cells and fetal tissue are still in early experimental stages. Controversial clinical trials using these same sources of stem cell lines are reportedly being conducted in several countries, some with little scientific or other oversight and no evaluation of clinical outcomes and safety.

Indeed, unproven stem cell interventions outside a clearly regulated clinical trial are proliferating around the world, facilitated by loopholes in several national regulatory systems or even encouraged by government support. Confusion between these unproven interventions and scientifically sound and rigorously designed clinical trials puts at risk not only the safety of research participants, but also damages the integrity of the field as it erodes public trust. Similar negative effects arise from the lack of transparency in disclosing the protocol design and its outcomes in a number of legitimate stem cell-based clinical trials and interventions.

In the field of stem cell research, the prospect of clinical trial registration has seldom been explored. This is inspite of a global consensus that recognizes the need for prospective registration of all interventional trials as a scientific, ethical and professional imperative (if not a legal obligation) for scientists, governments and funding organizations. This duty is grounded in the fundamental need to disseminate knowledge and protect and respect research participants, but also damages the integrity of the field as it erodes public trust. Similar negative effects arise from the lack of transparency in disclosing the protocol design and its outcomes in a number of legitimate stem cell-based clinical trials and interventions.

In order to be effective, clinical trial registries must be global, comprehensive, accurate, and publicly accessible. In addition, access to a registry should be simple, inexpensive and appropriate to the intended user population to allow for the unrestricted dissemination of research results. All these should be coupled with an independent verification of postings and compliance mechanisms in order to ensure that ethical standards in clinical practice are respected.

The raison d’être for the establishment of a CTR is to serve as a vehicle for knowledge transfer by providing an unbiased public record on safety and effectiveness, which in turn is translated in the foundation of evidence-based medicine. Moreover, by requiring the prospective registration of clinical trials at their inception, the problem of bias in the body of evidence could be largely eliminated, as registration in a CTR would occur independently of the ultimate findings or publication status of a trial. (Table 1)

Table 1: Clinical Trial Registry: Objectives

<table>
<thead>
<tr>
<th>Objective</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Respect the investigator-participant covenant to contribute to biomedical knowledge by making trial methods and findings public.</td>
</tr>
<tr>
<td>2.</td>
<td>Strengthen protection and respect for research participants</td>
</tr>
<tr>
<td>3.</td>
<td>Foster accountability and transparency with regard to global standards for ethical research.</td>
</tr>
<tr>
<td>4.</td>
<td>Provide a foundation for evidence-based medicine</td>
</tr>
<tr>
<td>5.</td>
<td>Serve as a vehicle for knowledge transfer by providing an unbiased public record on safety and effectiveness</td>
</tr>
<tr>
<td>6.</td>
<td>Advance innovation and acceleration of research practice in clinical therapies</td>
</tr>
</tbody>
</table>

*See for example the following national clinical trial registries: USA Clinical Trials.gov, Australian New Zealand Clinical Trials Registry (ANZCTR), Chinese Clinical Trial Register (ChiCTR), Clinical Trials Registry – India (CTRI), German Clinical Trials Register (DRKS), Iranian Registry of Clinical Trials (IRCT), Japan Primary Registries Network, The Netherlands National Trial Register (NTR), Sri Lanka Clinical Trials Registry (SLCTR)

**The WHO International Clinical Trials Registry Platform (ICTRP) overall objective is to ensure that a complete view of research is accessible to all those involved in health care decision making. This will improve research transparency and will ultimately strengthen the validity and value of the scientific evidence base”. The ICTRP was developed in collaboration with the International Standard Randomised Controlled Trial Number (ISRCTN) register, based in the UK, and the ClinicalTrials.gov registry, based in the US, the ICTRP with the aim to promote consensus regarding international norms and standards in clinical trial registration. The ICTRP requires that clinical trials are registered at inception and proposes that a unique Universal Trial Reference Number be given to each trial to prevent duplication. The ICTRP is not a registry itself but a comprehensive search portal for registries that exist worldwide. [http://www.who.int/ictrp/en/](http://www.who.int/ictrp/en/)
Furthermore, it is the goal of a CTR to enable to carry out meta-analyses. Meta-analyses or quantitative overviews are the primary means by which the safety and efficacy of new drugs and other interventions are assessed. Often individual clinical trials lack adequate statistical power to reliably adjudicate between alternative treatments strategies. It is therefore necessary in many instances to conduct meta-analyses or quantitative overviews of all relevant trials in order to draw conclusions about the efficacy of a particular treatment or procedure. To this date, the results of meta-analysis studies have improved clinical practice in many areas of medicine.

Stem cell research plays a key role in the increasingly promising area of regenerative medicine, showing potential to improve our ability to treat, prevent and cure disease by providing a potential unlimited source of cells for organ transplantation and therapies. Stem cell research could also provide a successful model system for drug discovery, including the development of new testing methods for efficacy, toxicity and safety. It will improve our understanding of the processes of human cell differentiation and development, with possible positive consequences for the treatment of diseases such as cancer. Finally, research using induced pluripotent cell (IPs cells) and somatic cell nuclear transfer (SCNT) will create patient-and-disease specific stem cell lines for research purposes and eventually, for safe and effective therapies.

### Table 2

**“The registration of all interventional trials is a scientific, ethical and moral responsibility”**. WHO International Clinical Trials Registry Platform (ICTRP)

<table>
<thead>
<tr>
<th>Key Word</th>
<th>Number of Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stem Cells</td>
<td>1837</td>
</tr>
<tr>
<td>Hematopoietic Stem Cells</td>
<td>470</td>
</tr>
<tr>
<td>Autologous Stem Cells</td>
<td>19</td>
</tr>
<tr>
<td>Cord Blood Stem Cells</td>
<td>03</td>
</tr>
<tr>
<td>Embryonic Stem Cells</td>
<td>03</td>
</tr>
<tr>
<td>Adult Stem Cells</td>
<td>18</td>
</tr>
<tr>
<td>Fetal Stem Cells</td>
<td>0</td>
</tr>
<tr>
<td>IPs</td>
<td>03</td>
</tr>
</tbody>
</table>

*The search was conducted on June 15th 2009. [http://www.who.int/ictrp/en/](http://www.who.int/ictrp/en/)

Transplantation of cells derived from pluripotent stem cells is still a highly innovative practice and consequently, a great degree of uncertainty exists with respect of weighing the benefit/risk ratio for such interventions. The advantages that pluripotent stem cells possess in terms of their capacity for self-renewal and differentiation; are paired with the immense challenge of establishing mechanisms to adequately control them in order to prevent negative effects such as tumor formation, excess proliferation, inappropriate differentiation, improper localization, among other serious adverse events. The potential for significant risks arising from these interventions are distinct from all other therapies. Accordingly, they warrant particular scrutiny with regards to their protocol design, conduct and analysis (e.g. type of cell, disease or condition concerned, control cases, participant enrollment, ethics approval, outcomes, follow-up, etc.); to say nothing about evidence of safety and efficacy. On this latter point, the recommendations issued in ISSCR’s Clinical Translation guidelines are illustrative. The guidelines call on “researchers to publish positive results, negative results, and adverse events and thus promote transparency, to prevent others from being subjected to unnecessary risk in future clinical research and to ensure the development of clinically effective and competitive stem-cell based therapies.”

The impact of trial registration of cell-based clinical interventions should not be taken lightly. The continuous and comprehensive registration of these interventions could significantly impact the foundation of evidence-based medicine, and even shape clinical practice by supporting the translation of research from the bench to the bedside through the development of best practice guidelines. To draft best practice guidelines – such as those adopted by ISSCR -, professional organizations rely on the body of scientific evidence; which in turn outlines the current standard of care. Similarly, policy-makers often rely on such evidence when drafting laws and regulations dealing with scientific and medical practice. As a result, clinical trial registration could have a great impact in shaping not only public policy, but also medical or product liability. The latter is of particular importance given the already mentioned proliferation of scientifically unproven and ethically problematic cell-based interventions.

The principle of benefit sharing provides an additional justification for advocating for the prospective registration of clinical trials. Clinical trials contribute to building society’s collective knowledge. The financial investments committed by sponsors of clinical research – especially when obtained by public funders – demand for the resulting knowledge to be shared by informing priority setting and the planning of future studies, identifying trends and gaps and avoiding unnecessary duplication (which must be distinguished from appropriate replication) of research.

Of equal importance are the objectives of respecting the investigator-participant covenant to contribute to biomedical knowledge by making trial methods and outcomes public. Most often, the participation of healthy volunteers in a clinical trial takes place because such individuals believe they are contributing to the generation of medical knowledge. However, when the knowledge gained is never transferred, the trust between investigators, research participants and the public at large is breached.

Fostering accountability and transparency with regard to global standards for ethical research is also a goal of clinical trial registration. A fundamental tenet of research ethics is respect for autonomy. For research participants to be respected as autonomous agents, they must provide free, voluntary and informed consent. The latter can only be achieved by publicly disclosing the body of evidence as pertains to trial findings (inconclusive, negative or positive), thus making explicit...
the current standard of care. This public record empowers research participants, enabling them to make informed decisions, especially with respect to the balancing of the benefits and risks of participation. It further mitigates the chances of therapeutic misconception. Strengthening protections for research participants in early stem cell-based clinical trials is necessary given the highly innovative nature of these interventions, and the likelihood that recruitment of research participants would be done from the most vulnerable populations (e.g. the severely ill).32

**Clinical Trial Registration: Challenges**

At the present time, registration of clinical trials is generally voluntary, making compliance mechanisms difficult to enforce. However, some national jurisdictions and international institutions have adopted policies making registration a compulsory requirement (e.g. USA, India, Australia, Argentina, European Commission, etc.). Unlike the World Health Organization’s Clinical Trial Platform, which is based on voluntary registration, the International Committee of Medical Journal Editors (ICMJE)33 mandates that any manuscript detailing clinical trial findings must be recorded in a publicly accessed registry before it can be published. The ICMJE, an organization which represents eleven renowned medical journals, has thus taken the initiative to prevent publication bias while giving researchers an incentive to register their trials.

In the stem cell research context, as previously stated, the ISSCR stopped short of calling for mandatory clinical trial registration of all stem cell-based clinical trials. It opted instead for calling for the publication of research findings via scientific conferences and peer-reviewed journals, thus confining – to a certain extent* – the dissemination of knowledge to professional circles. The timely publication of research findings is particularly important in a rapidly evolving field that has elicted so much hope, hype and polarized political, social and ethical debates. Dissemination of research findings in scientific circles (e.g. conference, journals) and trial registration should not be interpreted as excluding requirements but rather as having a complementary role. A clinical trial registry if adequately designed targets not only the scientific audience but also to the lay public, thus making information available to a wider audience.

The success of a clinical trial registry relies on its ability to meet the needs of the primary intended users, patients and other members of the public. But ultimately it depends on a willingness to contribute to a joint enterprise for the common good.34 In order to ensure compliance, institutional review boards should require clinical trial registration as a condition of approval35 and so institutional responsibility would be established.

Aside from implementing compliance mechanisms, the auditing, monitoring and oversight of existing registries are additional difficulties that must be overcome in order for clinical trial registration to be effective. Similarly, to maintain trust, safeguards to protect privacy and confidentiality of research participants and proprietary information should be established. A registry includes extensive data coming from multiple sources; it requires frequent updating to remain thorough and correct. Therefore, verification procedures must be enforced to ensure accuracy and quality assurance.

It is argued that clinical trials should be registered at all phases, even at inception, in order to ensure full disclosure. Without the registration of clinical trials at all phases, it would be impossible either to know adverse reactions or to assess safety and efficacy. The registration of early-phase clinical trials would ensure that the risks related to new interventions or treatments are publicly known, thus preventing ineffective or harmful interventions from continuing. If clinical trials are registered only after they have been completed and found to be favourable, or published, publication bias will result. Furthermore, requiring that clinical trials be registered at inception would prevent the loss of potentially valuable scientific information due to early trials that are often terminated for economic reasons.36

Particular challenges relate to the design and scope of a clinical trial registry for stem cell lines, especially concerning the establishment of a minimum dataset as it would require agreement on standard data elements. A mandatory, minimum data set fosters transparency and accountability by providing a comprehensive and transparent (non-promotional) posting of methodology and results. The currency and accuracy of the information in a prospective registry is of paramount importance. In the case of stem cell clinical trials, data must include information regarding the origin of the human stem cell lines, their derivation and culture methods and conditions, traceability requirements as well as their banking procedures.

Clinical trial registration still faces unyielding resistance from the pharmaceutical and biomedical industries. As these industries account for the majority of clinical trials sponsors, it is essential that these industries participate and comply with registration and publication standards. Their reluctance stems on the alleged adverse effect of increasing safety or protections for research participants, the protection of academic freedom and the exclusivity of research ideas; as well as on the dangers of international piracy and/or the disclosure of trade secrets.38 All of these factors could negatively target their therapeutic development and regulatory strategies, potentially damaging investor interests and stock value.39

The pharmaceutical and biotechnological industries concede that the dissemination of knowledge and the protection of the rights and the safety of patients (and research participants) should triumph over concerns for the confidentiality of proprietary interests, the protection of academic freedom and the exclusivity of research ideas.40 However, they argue that clinical trial registration would not have the effect of increasing safety or protections for research participants/patients nor of diminishing publication bias. It remains to be seen if a balance between those conflicting interests could be achieved in order to serve the public interest. As pointed out by Rennie, “the financial cost of an effective, independent and transparent clinical trial register would amount to a tiny fraction of the costs of the trials themselves, or the costs of not knowing their

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*ISSCR published along to the Guidelines for the Clinical Translation of Stem Cell, a Patient Handbook on Stem Cell Therapies (December 2008), providing valuable scientific information for patients and their doctors evaluating a stem cell therapy.*
results, while the personal costs of allowing the present chaotic system to continue are incalculable.”

Conclusion

History has taught us many cautionary lessons of significant harms arising from moving forward with a scientific field of inquiry without transparency and accountability. These harms go beyond physical harms to research participants, but they extend to ethical and moral ones that reach society and science itself, eroding public trust. Scientific research holds out much promise for potential social benefits for funders, research participants and society in general. However, this promise cannot be realized if research findings are concealed, selectively reported or misrepresented. The global consensus declaring the prospective registration of clinical trials a scientific, ethical and professional obligation is a major milestone. Yet, this recognition is insufficient in the absence of compliance. To date, voluntary schemes calling for publication and registration have met with limited success.

Prospective disclosure of research findings and clinical trial results fosters innovation and scientific rigor. As stem cell research rapidly evolves, bringing us one step closer to the clinic, the time is ripe to remind us all of the ethical duties we owe to society, to science and to ourselves. Hence, this renewed call for making clinical trial registration a mandatory requirement.

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Closely related to her academic work is her role as a policy adviser to government, professional and international bodies, such as the United Nations, where she played an active role in the adoption of the UN Declaration on Human Cloning. Most recently, she has contributed to the Bioethics Education Project of the Royal College of Physicians and Surgeons of Canada.

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Federal Funding of Stem Cell Research: Past, Present and Future

By Lawrence A. Soler, J.D.

On March 9, 2009 President Barack Obama signed an Executive Order expanding federal funding for research using embryonic stem cells in a White House signing ceremony packed with legislators, scientists, and people who have suffered from a range of diseases and medical conditions that could benefit from the research. The President’s executive order was a major milestone in the 10-year effort by those patients, scientists, academics, and others who have argued in support of a broader federal stem cell policy.1

In some ways, the most telling aspect of the ceremony was that when President Obama signed the Executive Order, numerous members of Congress were in attendance. Their presence signaled a significant shift in public opinion regarding the use of federal funding for embryonic stem cell research; further, it demonstrated the attitudinal changes regarding stem cell science that have taken place since 1998, when embryonic stem cells were first derived.

Today, for many Americans, stem cell science is viewed as potentially beneficial – not just for people suffering from disease – but in maintaining the country’s prominence and preeminence in scientific leadership. In a remarkably short timeframe, stem cell science has made the unusual transformation from a non-issue to a political hot button – and to an issue that transcends politics.

Background

Embryonic stem cells were first discovered in 1998 by Dr. Jamie Thomson of the University of Wisconsin and Dr. John Gearhart of the Johns Hopkins University.2, 3 While widely applauded for its potential in the scientific community, their discoveries very quickly set off a firestorm affecting researchers, ethicists, politicians and, most importantly, patients in the United States (US) and around the world. In fact, the first series of congressional hearings on the science followed quickly, beginning in January 1999, when the Senate Committee on Health, Education, Labor, and Pensions convened sessions involving a series of top researchers and ethicists.4

What became clear at the outset was that most US policymakers did not have an understanding of stem cell research and therefore were uncomfortable with the concept. Almost immediately, the source of embryonic stem cells became a key issue in the discussion and debate and initially there were broad misunderstandings about the origin of stem cells – with many assuming the issue to be associated with abortion.

At the time, relatively few legislators had a clear understanding of the reality; the stem cells at the center of the issue were cells derived from embryos created for in vitro fertilization (IVF) procedures. In fact, the cells in question were not going to be used and were slated to be discarded.

More often than not, the creation of embryonic stem cells was erroneously linked to abortion, and the corresponding political, moral, and religious issues that it entailed. To compound the problem, there were a handful of legislators and others that might have understood that abortion was not tied to stem cells, but did not have a detailed understanding of or were uncomfortable with the IVF process itself. As a result, the immediate political reaction to the 1998 Thomson/Gearhart discoveries leaned toward a ban on the research.

The Role of Patient Advocacy

In response to initial fears and negative reactions (often based on misunderstanding), an organized effort was launched on the part of patient advocacy groups to delay any potential federal ban on embryonic stem cell research. The aim was to provide education on the role of stem cells, the science, and their potential for therapies and cures for leading conditions. In addition, time was needed to enable discussion and debate related to surrounding ethical and religious implications. This effort started with Patient’s Cure, originally formed by Dan Perry, who was the Executive Director of the Alliance for Aging Research. Patient’s Cure’s major focus was to slow the momentum of any amendments that might surface in Congress restricting federal funding and support for stem cell research.

Patient advocacy in the area of stem cell research emerged among the campaign promises made by then Presidential candidate George W. Bush, who pledged to impose a ban on federal funding for embryonic stem cell research. Once elected, it was clear that a larger scale and more comprehensive effort would be required to preserve federal funding for the research – if not the ability to conduct stem cell research itself.

Formation of the Coalition for the Advancement of Medical Research (CAMR)

The result was the creation of the Coalition for the Advancement of Medical Research (CAMR). Today, CAMR comprises more than 100 nationally recognized patient organizations, universities, scientific societies, and foundations, and conducts advocacy and education outreach focused on developing better treatments and cures for people with life-threatening illnesses and disorders.