

Patients Beware: Commercialized Stem Cell Treatments on the Web

A report by the International Society for Stem Cell Research (ISSCR)'s Task Force on Unproven Stem Cell Treatments outlines development of resources for patients, their families, and physicians seeking information on stem cell treatments.

Introduction

The International Society for Stem Cell Research (ISSCR) is concerned that stem cell treatments are being marketed to consumers around the world without safeguards in place to ensure the safety or likely effectiveness of experimental treatments or truthfulness of claims about so-called proven therapies. These practices could place individual patients at risk and also jeopardize the progress of legitimate stem cell clinical translation. The ISSCR seeks to alert patients and their caregivers to these potential concerns and to answer the numerous enquiries received from patients and their advocates about clinics that claim to offer stem cell therapies.

The ISSCR Task Force on Unproven Stem Cell Treatments (hereafter the Task Force) was convened by the 2009–2010 President of the ISSCR, Dr. Irving Weissman, to formulate recommendations for the development of a web-based resource for patients, their advocates, clinicians, and associations in evaluating claims of benefit from advertised stem cell treatments. In particular, the Task Force was asked to propose a process for listing clinics or programs and whether they meet what the ISSCR deems to be minimum standards of assessing safety and efficacy and to define criteria to systematically evaluate clinics or programs for inclusion on such a list (Weissman, 2009). The members of the Task Force are listed in Table S1.

Here, we summarize the discussion and recommendations of the Task Force for the development of a web-based resource that includes: (1) listing of individuals, clinics, or other entities offering asserted stem cell therapies and whether they provide information showing that appropriate safeguards are in place; (2) resources that explain fundamental scientific principles of stem cell biology and the implications for stem cell treatments and outline the widely accepted process of clinical translation; and (3) a list of questions patients and caregivers should ask purveyors to aid them in making treatment decisions.

Why an ISSCR Initiative on Unproven Stem Cell Treatments?

The extraordinary promise of stem cells for future treatments of otherwise intractable diseases and conditions has raised great hope and expectations in patients, advocates, physicians, and researchers alike. Yet this excitement has led to unacceptable exploitation of patients' hopes and fears.

Through literature, clinician reports, patient questions, and patient complaints, the problem of misleading direct-to-consumer advertisement of stem cell therapies has become all too familiar to members of the Task Force, the ISSCR, local stem cell networks, and patient advocate organizations dedicated to disease-specific cures. Advertisements that claim to

offer proven and effective therapies for many diseases have sprung up in various forms relying on doubtful theories that neither peer nor public review, nor regulatory authorities, have verified. Indeed, a study of advertising on widely accessed websites demonstrated that the portrayal of likely clinical benefit is optimistic, overpromising results and underestimating the potential risks, and is unsubstantiated by peer-reviewed literature available to all scientists, medical professionals, and laypeople (Lau et al., 2008). Clinical outcome may be selectively displayed, methods kept secret and not subjected to independent scientific and clinical examination, and treatment offered outside of regulatory oversight. These so-called therapies therefore fail to meet minimum ethical, scientific, and medical standards that such oversight entails, including appropriate support through preclinical data; commensurability of risks and benefits; phased, structured assessment of safety, efficacy, dosing, or appropriate administration; and independently assessed and approved informed consent.

Furthermore, in some situations, large amounts of money are being charged for apparently unsubstantiated therapies, a further departure from widely accepted norms. Authorization to market a medicinal product is typically sought from a national or supranational regulatory agency only after rigorous testing through a formal process of clinical trials has established safety and efficacy. In a formal clinical trial setting, it is not common practice for the provider to charge for the experimental treatment, rather costs of the experimental treatment and trial monitoring is often defrayed by the company developing the treatment or by local or national government funding.

A problem of these dimensions calls for more than the actions of any one organization or agency, and certainly more than the actions of one scientific society such as the ISSCR. Yet, the ISSCR recognizes the essential relationship that exists between scientific progress and public responsibility. In previous reports ("Guidelines for the Conduct of Human Embryonic Stem Cell Research" and the "Guidelines for the Clinical Translation of Stem Cells"), the ISSCR addressed the broader social, ethical, and legal implications in addition to setting professional standards for research conduct and clinical application (Daley et al., 2007; ISSCR, 2006; ISSCR 2008a; Taylor, 2007; Hyun et al., 2008). The latter guidelines include a stand-alone appendix, a "Patient Handbook on Stem Cell Therapies" to directly address the concerns of patients (ISSCR, 2008b).

This current effort therefore grows out of the long-standing commitment of the ISSCR to ethical and scientific self-regulation through globally representative consensus on standards that distinguish sound and ethical stem cell science from practices that would be unethical or unsound. The Task Force believes

the ISSCR plays a catalytic role in engaging with other organizations and the public to address social, ethical, and legal implications of scientific progress. The ISSCR's aspirations for public benefit through increasing knowledge entail this commitment: to avoid overstating what is currently known, whether in the scientific domain, the clinical domain, or the commercial domain. In fact, clinics and suppliers making unproven or exaggerated claims may endanger patients, and through poor or reckless practice they potentially discredit the field itself and threaten to impede the progress of legitimate clinical translation. The Task Force believes that the ISSCR has an appropriate role in working with others to address such clinics and suppliers and to educate professionals and patients as to responsible pathways of clinical translation. We therefore endorse the President's initiative and commend the ISSCR for its willingness to undertake such a step.

The ISSCR is a scientific and medical society with unique knowledge of a still-developing scientific frontier and specialized expertise in the necessarily careful pathway from basic scientific knowledge to patient benefits through responsible clinical translation. The Task Force members reflect this expertise and have brought to this effort a great diversity of perspectives—researchers, clinicians, ethicists, jurists, and patient advocates. The Task Force provides the recommendations within this report after much discussion and consideration, for the establishment of a feasible methodology for ISSCR action while maximizing the value of information made available to patients and their advocates.

2008 ISSCR Guidelines: Defining the Appropriate Pathway from Basic Scientific Knowledge to Clinical Applications

The ISSCR published "Guidelines for the Clinical Translation of Stem Cells," which define a pathway for the responsible development of safe and effective stem cell therapies (ISSCR 2008a). In that report, the Task Force on the Clinical Translation of Stem Cells recommended that development of stem cell therapies occur primarily through structured clinical research trials, which, under internationally accepted standards, are subject to independent and ongoing assessment of their scientific and ethical soundness by ethical review boards and government agencies.

These guidelines recognized that progress, especially in surgical treatment, has occurred through innovation outside clinical research trials (Section 7: Stem Cell-Based Medical Innovation). However, respect for innovation has never meant that patients' urgent needs justify scientifically reckless or unethical acts. Innovation outside research requires, among other things, that the scientific and clinical plausibility for an innovative approach is demonstrable; that patients can weigh known and possible risks against realistic descriptions of potential benefits; that alternative treatments are clearly communicated; that there is independent review and oversight; and that clinical supports are in place to address known and unanticipated risks. The guidelines also noted that certain characteristics of stem cells required that their development as medical interventions called for special care and "underscore the need for independent expert peer review prior to clinical investigation to ensure the integrity of the research and informed consent processes" (Section 1: Introduction).

The Task Force on the Clinical Translation of Stem Cells felt strongly that the innovation exception does not justify the commercialization of stem cell-based interventions without credible rationale or oversight or without a commitment by practitioners to use this experience to contribute to a general body of knowledge through the communication of outcomes, including negative outcome or adverse events, to the scientific community for critical review and by moving to a formal clinical trial in a timely manner. Indeed, the guidelines "recognize[d] a distinction between the commercial purveyance of unproven stem cell interventions and legitimate attempts at medical innovation outside the context of a formal clinical trial. Responsible clinician-scientists may have an interest in providing medically innovative care to a few patients using stem cells or their derivatives prior to proceeding to a formal clinical trial," and the peer-reviewed scientific and medical case, together with the patient's informed choice among limited alternatives, may justify it in certain cases.

The Task Force on the Clinical Translation of Stem Cells therefore concluded, and the ISSCR Board of Directors agreed, that the primary pathway for translating scientific advances into therapies ought to be the well-established route from peer-reviewed science to ethically and scientifically reviewed clinical research trials under appropriate regulatory oversight.

Defining the Problem

To establish which aspects of medical practice might be assessed by objective review and examination of publicly available materials and direct contact, and what kind of information might be useful to those seeking treatments, the Task Force first discussed concerns about the commercial practice of unproven stem cell interventions.

We eliminated aspects of practice that do not represent the primary problem. First, we noted that the concern is not about medical tourism in which citizens of one country travel to another country for treatments offered uniquely or more cheaply. The problem of unproven stem cell treatments occurs in many countries, and whether abroad or at home, the absence of essential clinical supports and follow-through can expose patients to serious health risks. Thus, although some medical tourism raises special concerns, and some issues with questionable clinics and suppliers involve medical tourism, the problems are not identical nor necessarily coincident (Cohen, 2010).

The concern is also not simply the attempt to treat diseases for which there is no scientifically proven stem cell-based therapeutic solution. This view of the problem is too broad, for it would treat legitimate clinical research as being identical to the sale of unproven treatments. Furthermore, to simply define treatable and untreatable conditions and to use this as a criterion for listing a given entity would require the ISSCR to be omniscient with respect to all new developments, including proprietary ones.

A fundamental principle espoused by previous ISSCR guidelines and reiterated by this Task Force is transparency: a willingness to communicate openly with the scientific and medical community, with regulators and with patients. This task force had enormous concern about medical practices where evidence of this communication was missing—where there was a lack of openness concerning methods and results, lack of peer review, inaccurate portrayal of scientific plausibility, unclear expertise of practitioners, and lack of independent oversight. These issues

are also of direct relevance to patients and families, not just to those who would base their choice on scientific and ethical soundness, but also those who, less persuaded by such factors given the failure of existing therapies, would nonetheless be concerned with the truthfulness of solicitations with their own medical vulnerability to matters becoming even greater through unknown risks and unaddressed adverse events.

We see a widely accepted imperative to report research and clinical findings and to subject results, methodologies, and conclusions to the scrutiny of independent experts in the field. The practice of external peer review has long been held as the foundation of biomedical publication and used as a method to assess the rigor of scientific enquiry and to minimize unwarranted claims or overinterpretation of data prior to broad circulation. Replication of data by independent groups is a key indicator that the data are robust— that the findings and conclusions are likely to be valid and that the technology can be repeated in someone else's hands. Thus, robustness of data might be evaluated by (1) direct relevance of the data to the specific disease and treatment in question; (2) publication by groups working independently of each other; (3) publication of results, methodologies, and conclusions; and, (4) as an indication of peer review and basic scientific quality, inclusion in the MEDLINE database, a freely available and well-recognized database of articles from journals that observe prescribed publication procedures compiled by the United States National Library of Medicine (NLM) (US NLM, 2007).

The Task Force also affirmed previous statements and reports from the ISSCR and other international bodies that only when compelling preclinical data are available is careful and incremental testing in patients justified, and then such testing is always subject to rigorous and independent scientific and ethical oversight.

Through these deliberations, the Task Force identified core elements that reflect a commitment to transparency in operations and a commitment to the widely recognized translational trajectory noted above. These elements do not incorporate all criteria identified as important by the Task Force for assessing safety and likely efficacy. They do, however, provide an objective minimum level of transparency of practice and independent scientific, ethical, and regulatory oversight.

1. The clinical investigations from the early trials to commercialization have been conducted under the guidance and authority of an independent oversight body that adheres to internationally accepted ethical guidelines for the protection of human subjects, including assessment that the risk to patients was not greater than the possible benefits and that the patient or the patient's parents or legal guardians understood and gave informed consent for the medical procedure to take place.
2. The clinical investigations from the beginning to commercialization have been overseen and authorized by a national or supranational regulatory body or bodies for safety and efficacy.

Recommendations ***Inquiry and Review Process***

The Task Force recommends that the ISSCR establish an inquiry and review process to look into clinics and suppliers

promising therapeutic benefits from the administration of preparations claimed to contain or be constituted of stem cells and/or their induced derivatives. The guiding principles for the development of the recommended process were that (1) the standards for identifying and reviewing clinics and suppliers should be objective and clear; (2) the inquiry and review process should be publicly transparent and relatively straightforward for any clinic or practitioner to comply with; (3) conflicts of interest, if any, of the declarant ought to be disclosed to the ISSCR; (4) there should be no actual or apparent conflicts of interest of staff or others involved in the inquiry or review process for any particular matter; and (5) any findings that a clinic fails to meet standards should be communicated in a specific factual way, rather than with broad conclusions of fraudulent practices.

Four main steps are outlined for the inquiry process:

1. Identification of the clinics to be contacted about their practices. The process should be open to identification of entities for examination from a broad and unbiased range of sources, such as patients and external groups and requests by ISSCR members. Inquiry should be pursuant to a standardized online intake process, such as that on the draft intake form (Figure S1 available online).
2. Preliminary review of advertising and solicitation materials of the clinic or supplier, such as Web materials, to determine whether the entity is involved in or claims to be involved in the purveyance of stem cell therapy, or the supply of stem cells or other stem cell-related service where there is claim/implication of therapeutic benefit.
3. Contact with the clinic or supplier to request information aligned with the elements of inquiry discussed below (see Figure 1). The entity will be subjected to scrutiny for each disease encountered on the advertising or solicitation materials. At the time of this publication, entities will be excluded from the search in which the information available is not provided in English or lacks a translation into English. The Task Force recommends translations of advertising materials to English be incorporated into the inquiry process over time. Entities will also be excluded from the search in which the only clinical applications cited are (1) bone marrow, cord blood, or other blood stem cell populations used to treat diseases/conditions of the blood-forming or immune systems (including the treatment for compromised hematopoiesis secondary to high dose chemotherapy for cancers) or (2) epidermal stem cell therapies for burn trauma or limbal stem cells for corneal replacement.
4. Review and results publication. Materials received will be reviewed as objectively as possible against the inquiry elements, discussed below. The meaning of the results ought to be self-evident from a clear description on the ISSCR Web site of the precise processes and criteria used. Interpretation and subjective conclusions should be avoided in any presentation of the data.

Elements of Inquiry

The Task Force recommends that the inquiry and review process ask for evidence that the entity under review adheres to the

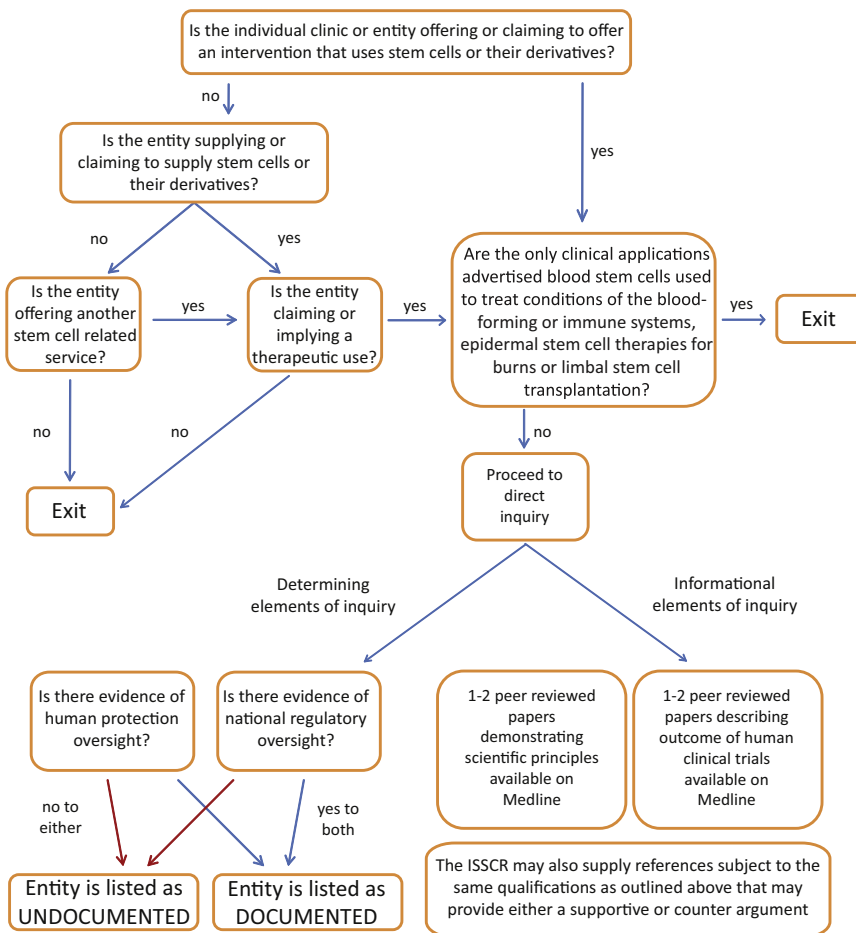


Figure 1. Schematic of Inquiry and Review Process for Listing Stem Cell Treatment Providers

The inquiry and review process recommended by the task force is depicted graphically (see text for details). A preliminary review of advertising materials brought to the attention of the ISSCR will determine whether a direct inquiry will be made to the entity. Entities advertising stem cell treatments or claiming clinical efficacy of stem cell products for applications outside of the blood system, epithelial stem cell treatments for burns, or limbal stem cell treatments for corneal repair will be asked for evidence that (1) a medical ethics committee was involved to protect patients' rights and (2) appropriate regulatory oversight was in place. The entity will be listed as "documented" or "undocumented" on the basis of whether or not they provide these elements. Undocumented clinics that claim to be practicing innovative medicine will be listed with a statement indicating the ISSCR Task Force position on innovative medicine (see text for details). Citations to relevant literature may be included with the Web site listing; the entity is invited to provide relevant robust publications and the ISSCR may also provide such publications offering a supportive or counter argument. See also Table S1 and Figure S1.

The ISSCR may contact the signing individual identified in an effort to confirm that the applicant, protocol/project, and approval are asserted accurately.

widely accepted translational pathway from basic science to clinical applications. The following elements do not incorporate all of the important criteria identified by the Task Force for assessing safety and likely efficacy, nor do they allow the judgment of relative anticipated effectiveness. They do, however, provide an objective minimum level of transparency of practice and independent review.

Determining Elements of Inquiry. Clinics and suppliers should be asked to provide evidence of the following for a given treatment for a given disease or condition offered in the context of a research study (clinical trial), experimental therapy, or claimed proven therapy:

1. Evidence of review and approval for human subjects protection by an independent committee or agency such as an Institutional Review Board or Ethics Review Committee established under internationally accepted ethical guidelines; including at a minimum:
 - Name of applicant/principal investigator
 - Title of protocol/project
 - Committee name and/or identifying number
 - Date of approval
 - Name of signing individual
 - Contact information for signing individual

2. Review and authorization or approval by relevant supranational or national regulatory authorities such as the European Medicines Agency (EMA) or the US Food and Drug Administration (FDA) for clinical trial or, where applicable, reimbursed therapies/commercial use based on data provided by the clinic or others under supervised trials; or evidence of exemption from review.

The ISSCR may contact the relevant regulatory authority in an effort to confirm that the information provided is complete and accurate.

These determining elements of inquiry stated above—review for human subjects protection and regulatory oversight—should direct the ISSCR in listing clinics.

Informational Elements of Inquiry. Clinics and suppliers should be invited to submit to the ISSCR examples of preclinical and clinical research published in the peer-reviewed literature:

1. Up to two published articles from groups, ideally working independently of each other, demonstrating the scientific principles for use of a given cell product for the specific disease.
2. Up to two published articles demonstrating the outcome of human clinical trials for both safety and efficacy.

Articles should be peer reviewed, include data of direct relevance to the specific disease in question, include results,

methodologies, and conclusions, be written in English, and be included in the MEDLINE database. The entire article should be provided to the ISSCR.

Output—A Web-Based Resource

The Task Force recommends a web-based resource that includes the parts outlined below. Together, these should allow a patient on their own, or in consultation with their health care provider, to consider whether the approach taken by a clinic of interest might lack the scientific rigor, transparency, and independent oversight and regulation the ISSCR and others advocate.

1. *An online intake mechanism.* A brief form that can be used by any individual to submit an entity to the ISSCR for formal inquiry.
2. *Results of inquiry.* The Task Force recommends two listings be developed that separately include those entities that do and do not provide upon request evidence of both of the above determining criteria (review for human subjects protection and regulatory oversight) in a timely manner and on a disease-by-disease basis. A review will be made for each disease encountered on the advertising or solicitation materials, except where excluded as outlined in the inquiry process. Thus, an entity may be included on a given list multiple times or for only a subset of the diseases for which they claim a stem cell-based treatment. The names of clinics currently under review will not be disclosed.

The information used for the inclusion of an entity on one or the other of these lists is provided by that entity. The ISSCR will not be responsible for the accuracy of claims.

- A. *Listing of clinics that do not provide evidence of both human subjects and regulatory oversight (the determining inquiry elements): “undocumented.”* Those entities that do not provide the information pertaining to human subjects and regulatory oversight requested of them should be listed as “undocumented.” The listing will be prefaced with an explanatory statement that describes the process and clearly indicates that:
 - i. The listing of an entity does not imply either ISSCR approval or disapproval, rather that specific elements of inquiry have not been adequately addressed.
 - ii. Similarly, absence of an entity or removal of an entity from listing does not imply ISSCR approval.
 - iii. No conclusion can be drawn from the absence of an entity/disease from this listing as the process is such that if an entity is not listed it may mean one of three very different things: no inquiry has been made; the inquiry is still in process; or the clinic has addressed each of the elements of inquiry.

If an entity is listed here and then subsequently provides information that addresses missing required elements, its name will be removed from this listing. Where the entity responds that they no longer offer treatment for a disease that has been previously advertised or offered, its name will be removed from this listing but a footnote will be included that the clinic no longer treats this disease. Entities that do provide evidence of both of

the determining elements of inquiry requested will be included on an independent listing as outlined below.

- B. *Listing of clinics that do provide evidence of the determining inquiry elements: “documented.”* Where evidence is provided that both human subjects and regulatory oversight are in place, clinics will be listed as “documented.” Again, this listing should in no way imply either ISSCR approval or disapproval, rather that the information requested has been provided. Thus, as for the previous listing, no conclusion can be drawn from the absence of an entity/disease from this listing as the process is such that if an entity is not listed it may mean one of three very different things: no inquiry has been made, the inquiry is still in process, or the clinic did not provide evidence to satisfy that both elements were addressed.

Approval by the appropriate independent human subjects oversight body and regulatory agency reflects only that certain ethical and legal obligations, respectively, have been met in the given locale. There is significant global diversity in what circumstances a regulatory agency may grant approval or provide exemption of review for a given product and what processes and standards are applied during review. Assessment of when a particular therapy is ready to move into clinical trials or from clinical trials to a more widely available treatment outside of trials may take into account a range of factors not necessarily applicable to other regions including the current standard of care treatment or prevalence of a disease or condition in the local population.

To provide additional information for caregivers or others interested, the listing will document relevant publications provided by the entity as outlined above (“Informational Elements of Inquiry”). Citations will be provided or, where the paper may be freely disseminated without breach of copyright, a pdf copy may be attached. The ISSCR may also supply up to two references subject to the same publishing qualifications outlined above that may provide either a supportive or counter argument.

There is necessarily a significant period of time from when the intake sheet is filled out requesting the ISSCR investigate a specific clinic until a final determination is made, estimated at 4–5 months. The Task Force recognizes that, particularly at the beginning before they are well established, the data listings will not address the concerns of an individual patient or their advocates looking to make immediate decisions. In addition, the criteria assessed do not address the complexities of information needed for an individual medical decision, although their absence portends a failure to respect known, widely accepted, fundamental standards.

Therefore, we recommend that the following resources be included on the Web site.

3. *Resources that explain fundamental scientific principles of stem cell biology and the implications for stem cell treatments and outline the widely accepted process of clinical translation.* Understanding key aspects of stem cell biology and what is realistic to expect from stem cell treatment might aid a patient and their caregiver in determining

where claims of efficacy may be exaggerated. For example, tissue-specific stem cells are limited in their potential and largely form the cell types found in the tissue from which they are derived. Thus, it is unlikely that a single cell type could be used to treat a multitude of unrelated diseases that involve different tissues or organs, and a patient should be wary of a clinic that makes such claims. Likewise, understanding the implementation of clinical trials and ultimately the commercial availability of a medicinal product, and the provisions for patient protection demanded by ethical oversight committees and regulatory bodies throughout this process, might make clear where there are concerning departures from widely accepted practice. For example, high cost of an experimental treatment might raise an immediate red flag to consumers that very careful investigation is required.

4. *Further questions a patient, if possible working with their caregiver, should ask the provider as part of evaluating the clinic and treatment they are considering.* Transparency and forthrightness are owed to any patient considering a potential therapy; indeed without it there can be no actual informed consent. A potential patient ought to be able to consult their own personal caregiver before making a choice and involve their own local caregiver in after-care if they wish. Furthermore, for any patient, even a patient undergoing well-accepted therapy, the clinical environment is critical. The list of questions provided by this document should assist a patient in evaluating such parameters.

Innovative Medicine Statement

The Task Force on Unproven Stem Cell Treatments agreed with the recommendations for practicing innovative medicine made by the ISSCR's Task Force on Clinical Translation of Stem Cells that application of medical innovation in the stem cell field should be confined to a very limited number of cases, should be subjected to external review and stringent oversight, and should move quickly toward a formal research study. Indeed, this Task Force argued that medical innovation be limited to no more than two participants. Therefore, we recommend that if the entity advertises an experimental or innovative medicine, the same inquiry process be applied.

Whether in advertising or solicitation materials, or in response to the ISSCR's inquiry, if an entity states that a therapy being offered is experimental or innovative and therefore does not need to have been tested in clinical trials or does not need the human subjects protection or regulatory oversight, the clinic will be listed with the following annotation:

The position of the ISSCR Task Force is that the provision of an untested experimental or innovative therapy to more than two participants is a departure from recommended practice and should be tested in a regulated and authorized clinical trial prior to being offered for sale.

Outreach

The Task Force recommends that its report be publicly presented. Posting of this report on the ISSCR Web site and through the ISSCR pages of affiliated journal *Cell Stem Cell* have both been useful devices in the past, and we endorse them here.

In addition, we recommend active engagement of other stem cell networks and consortiums and patient advocacy groups that could play a key and complementary role in disseminating information on this and other work that addresses fraudulent clinics or suppliers of stem cells and in framing the combined set of actions in a way that is understandable and useful to patients and to those who will receive their queries and requests for help.

The ISSCR should offer the educational resources and information offered on the Web site in additional languages wherever possible. To date, working with stem cell network partners, the ISSCR offers the "Patient Handbook on Stem Cell Therapies" in English, German, Italian, and French. Japanese and Spanish translations are planned.

We also strongly support working with the press in various countries to explain the problem, the approach we take, the potential role of other partners, and, indeed, the potential role the press itself could play in helping all of us avoid hyped discussion of stem cell "therapies."

This concludes the recommendations of the Task Force.

SUPPLEMENTAL INFORMATION

Supplemental Information includes one table and one figure and can be found with this article online at doi:10.1016/j.stem.2010.06.001.

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