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Guidelines for stem cell science and clinical translation

SUNIL K PANDYA

The International Society for Stem Cell Research has released its updated guidelines for stem cell research in order to provide "assurance that stem cell research is conducted with scientific and ethical integrity and that new therapies are evidence-based." The guidelines were updated by a Guidelines Update Task Force consisting of twenty-five scientists, ethicists and experts in healthcare policy from nine countries. The chairpersons of this task force are Jonathan Kimmelman, George Daley and Insoo Hyun. There is no representative from India, the only person of Indian origin on it, Mahendra Rao, represents The New York Stem Cell Foundation.

A study of these guidelines shows us how unscientific and unsupervised the usage of stem cells in clinical practice is in India. We desperately need immediate corrective action with implementation of these or similar guidelines and strict and severe punishment of all those flouting them. The full force of government and judiciary must back the application of these guidelines.

The lack of such guidelines is luring innumerable patients and their families to questionable, unscientific and unethical practices, usually at great cost and at times to their financial ruin, without any proven benefit.

The very first section of the guidelines deals with *Fundamental ethical principles*. It defines the primary goals of stem cell research as the advancement of scientific understanding and the generation of evidence for addressing unmet medical and public health needs. "**This research should be overseen by qualified investigators and coordinated in a manner that maintains public confidence…Key processes for maintaining the integrity of the research enterprise include those for independent peer review and oversight, replication and accountability at each stage of research."** (Emphasis added)(1: p 3).

This section also emphasises the primacy of patient welfare. "Physicians and physician-researchers owe their primary duty to the patient and/or research subject… Application of stem-cell based interventions outside of formal research

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settings should be evidence-based, subject to independent expert review and serve patients' best interests. It is a breach of professional medical ethics to market and provide stem cell-based interventions to a large patient population prior to rigorous and independent review of safety and efficacy."(1: p 4).

On transparency, the guidelines insist that researchers "should convey the scientific state of the art, including uncertainty about the safety, reliability or efficacy of potential applications."(1: p 4).

Discussing social justice, the guidelines emphasise that "costs of proving the safety and efficacy of a medical intervention be borne by entities that are expressly privileged to profit when such entities are marketed. Where cell-based interventions are introduced into clinical application, their use should be linked to robust evidence development."(1: p 4)

Section 2 deals with laboratory-based research including the use of tissues obtained from embryos.

Section 3, *Clinical translation of stem cells*, reiterates principles enunciated in Section 1. "In most countries and jurisdictions, the use of cellular products for medical therapy is regulated by governmental agencies to ensure the protection of patients…"(1: p 18). It emphasises the risks attending even minimal manipulation of cells outside the human body. Discussions on sourcing of stem cells, manufacture of cellular derivatives, preclinical studies precede general considerations. The need for rigorous demonstration of safety and efficacy in preclinical studies is emphasised. "More stringent design and reporting standards should be demanded where planned trials involve human research subjects with less advanced disease, when invasive delivery approaches are anticipated or, where the cell product presents greater risk and uncertainty."(1: p 23).

The need for assessing the risks for tumorigenicity, detailed and sensitive biodistribution studies of cells and addressing long-term risks is highlighted. Compelling preclinical evidence in well-designed studies must precede any clinical trial, small and large animals being used where necessary, the latter being preferred.

"**Sponsors, researchers and clinical investigators should publish preclinical studies in full and in ways that enable an independent observer to interpret the strength of the evidence supporting the conclusions…**" (1: p 28). **"All studies involving clinical application of stem-cell based interventions must be subject to prospective review, approval and ongoing monitoring by independent human subjects review committees"** (1: p 29). **"Researchers should promptly publish aggregate results regardless of whether they are positive, negative or inconclusive. Studies must be published in full and according to the international reporting guidelines."** (1: p 38) (Emphasis in original text).

The warning, reproduced in full below, is especially relevant to India:

"WARNING ON THE MARKETING OF UNPROVEN STEM CELL-BASED INTERVENTIONS: The ISSCR condemns the administration of unproven stem cell-based interventions outside of the context of clinical research or medical innovation compliant with the guidelines in this document and relevant laws, particularly when it is performed as a business activity. Scientists and clinicians should not participate in such activities as a matter of professional ethics. For the vast majority of medical conditions for which putative "stem cell therapies" are currently being marketed, there is insufficient evidence of safety and efficacy to justify routine or commercial use. Serious adverse events subsequent to such procedures have been reported and the long-term safety of most stem cell-based interventions remains undetermined. The premature commercialization of unproven stem cell treatments, and other cell-based interventions inaccurately marketed as containing or acting on stem cells, not only puts patients at risk but also represents one of the most serious threats to the stem cell research community, as it may jeopardize the reputation of the field and cause confusion about the actual state of scientific and clinical development. Government authorities and professional organizations are strongly encouraged to establish and strictly enforce regulations governing the introduction of stem cell-based medical interventions into commercial use." (1: p 39).

A study of the "research" on and clinical usage of stem cells at each of the many stem cell centres in India using the criteria laid down in these guidelines will yield very useful data, much of it eye-opening. We lack legal notification of our regulatory authorities for stem-cell research and clinical usage. Agencies currently monitoring and funding medical research in India lack the power and the ability to investigate wrong-doing, much less punish and discipline wrong-doers.

A detailed study of this important document by those in power in government, our research agencies and organisations and by every clinician likely to consider the use of stem cells in any form is mandatory.

Reference

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