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Title

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Permalink

<https://escholarship.org/uc/item/8741s8px>

Journal

Stem Cell Reports, 16(6)

ISSN

2213-6711

Author

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Publication Date

2021-06-01

DOI

10.1016/j.stemcr.2021.05.011

Peer reviewed

ISSCR's Guidelines for Stem Cell Research and Clinical Translation: Supporting development of safe and efficacious stem cell-based interventions

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<https://doi.org/10.1016/j.stemcr.2021.05.011>

The ISSCR's revised Guidelines for Stem Cell Research and Clinical Translation reflect the organization's commitment to opposing premature commercialization of stem cell-based interventions and supporting the development of products that meet stringent ethical, scientific, and regulatory standards. The Guidelines contain five important new recommendations concerning clinical translation of stem cell products.

Introduction

With the release of its revised [Guidelines for Stem Cell Research and Clinical Translation](#), the International Society for Stem Cell Research (ISSCR) has revised, expanded, and refined its efforts to support the development of safe and efficacious stem cell therapies that meet rigorous ethical, scientific, and regulatory standards while opposing premature commercialization of stem cell-based interventions. A task force composed of numerous working groups contributed to the development and clarification of general principles, standards, and practical recommendations intended to help guide and shape the global conduct of stem cell research as well as the clinical and commercial translation of stem cell treatments. The author of this piece was a member of Working Group Four, a committee tasked with addressing regulatory issues and the global harmonization of regulatory standards; economics, pricing, and equitable access to stem cell products; and responsible public representations in stem cell research and scientific communication.

The ISSCR Guidelines do not have the force of law and are not enforced by regulators. Rather, they are intended to serve as transnational standards that can play a valuable role in informing the development and application of national regulations as well as providing scientists with clear and reasonable guidance concerning

how to pursue stem cell research and clinical translation in a responsible manner that complies with moral, scientific, and legal norms (Daley et al., 2016). Developing such global standards is crucial in a world where scientific research crosses borders and substantial regional variations in applicable laws can promote regulatory arbitrage, with problematic commercial and clinical activities drawn to jurisdictions with the weakest regulatory standards and oversight mechanisms (Sipp and Sleeboom-Faulkner, 2019).

Accompanying the gradual development of evidence-based cell therapies that have been approved by national regulators and have entered the professional standard of medical care is the emergence of a global marketplace in which businesses sell unlicensed and unproven stem cell products for wide range of clinical indications (Berger et al., 2016). Patients are drawn to such clinics by misleading advertising claims; widespread "hype" that assigns near-magical properties to stem cells; the sense of fear and desperation that sometimes accompanies being diagnosed with life-threatening or life-altering medical conditions; hope that they can receive effective treatments for their diseases, injuries, and painful symptoms; and other factors. The marketing and administration of unlicensed and unproven stem cell products sold on a direct-to-consumer basis

has resulted in fatal outcomes, serious injuries, substantial loss of personal savings, and other significant harms to patients (Berkowitz et al., 2016; Julian et al., 2020). Widespread marketing of purported stem cell treatments has also generated considerable public confusion concerning how to distinguish between cell-based products backed by substantial evidence of safety and efficacy and unproven stem cell-based interventions.

The ISSCR's efforts to develop Guidelines for Stem Cell Research and Clinical Translation

For more than a decade, the ISSCR has played an important role in supporting the development of stem cell therapies backed by substantial evidence of safety and efficacy generated in well-designed, rigorously conducted, and carefully controlled clinical trials (Hyun et al., 2008). Accompanying this concerted effort to promote the development of stem cell treatments that meet demanding scientific, ethical, and legal standards, the ISSCR has supported public understanding and patient safety initiatives intended to help research participants, patients and their loved ones, policy-makers, and other parties distinguish credible research activities and evidence-based stem cell therapies from exploitative marketing claims and problematic commercial activities and research practices (Taylor et al., 2010). The ISSCR has also played an important





role in articulating global standards for the conduct of all stages of stem cell research as well as the clinical translation of stem cell therapies. The development of such transnational standards has involved stem cell researchers from many different countries. The process has included contributions from health law scholars, science policy specialists, bioethicists, social scientists, and researchers from other scholarly fields. In addition to expecting its members to comply with these standards, the ISSCR has played an advocacy role in helping countries develop comprehensive, scientifically and ethically informed regulations applicable to cell- and gene-based therapies. The ISSCR has also assisted national regulatory bodies by identifying and addressing gaps and areas of interpretive uncertainty where such regulations already exist but are not comprehensive or are inadequately enforced. The ISSCR's updated Guidelines advance the organization's record of supporting the careful, evidence-based development of stem cell-based interventions. In particular, five new recommendations are worth noting.

Premature commercialization of stem cell-based interventions and the revised 2021 ISSCR Guidelines

First, government authorities, professional organizations, and other involved parties should develop and effectively enforce clear, comprehensive, and consistent policies and regulations governing the marketing and administration of stem cell-based medical interventions. Organizations such as national and transnational regulatory bodies that oversee the testing and approval of drugs, biologics, and medical devices; colleges and boards responsible for the licensure of physicians and other health care workers; and agencies responsible for ensuring truthfulness in advertising should all play important roles in overseeing the clinical translation

and commercial use of stem cell-based medical interventions. They have a particularly significant part to play in investigating and, where appropriate, taking regulatory action and other legal measures in cases where stem cell-based interventions lack substantial evidence of safety and efficacy, have not been approved for use or otherwise responsibly introduced into clinical practice, and have instead been prematurely commercialized using misleading advertising claims (Marks and Gottlieb, 2018; Marks et al., 2017).

Second, stem cell-based interventions, tissues, and cell- and tissue-based products that have been substantially manipulated or are used in a nonhomologous manner must be subjected to regulatory review and proven safe and effective for specific intended uses before they are marketed to patients or introduced into the routine practice of medicine. In brief, substantially manipulated cells and tissues have undergone processing or manufacturing steps that alter their original structural or biological characteristics. Cells and tissues are used in a nonhomologous manner when they are repurposed and perform a different basic function in the recipient than the cells or tissues originally performed before they were removed, processed, and transplanted, transfused, or otherwise delivered. The ISSCR acknowledges that some cell- and tissue-based interventions including skin grafts and minimally manipulated fat grafts used in a homologous manner need not be regulated as drugs, biologics, or advanced therapy medical products requiring premarketing review and approval by legally authorized national regulators or comparable governance bodies. Cells and tissues that have been minimally manipulated, are used in a homologous manner, and are transferred during the same surgical procedure do not pose the same degree of risk to patient safety

and public health as products that are substantially manipulated, are used in a manner that does not constitute homologous use, or are not transferred during a single surgical procedure. The ISSCR's updated Guidelines note these justifiable exceptions to cell-based products requiring extensive testing in clinical trials and premarketing authorization by legally empowered regulatory bodies. The Guidelines also note the importance of ensuring that these exceptions are well-defined and do not become regulatory loopholes or gray zones that businesses exploit in an attempt to avoid being subject to more rigorous standards for testing and approval (Sipp, 2017, 2019).

Third, novel stem cell-based interventions should only be introduced into routine clinical use following demonstration of substantial evidence of safety and effectiveness in well-controlled, appropriately powered clinical trials that result in statistically significant findings. There should be limited exceptions to this standard for rare diseases, such as life-threatening medical conditions, and other unmet medical needs for which there are no safe and efficacious therapies. In these circumstances regulators must consider the acceptable balance of risk and clinical benefit appropriate to particular medical conditions and patient populations for which novel interventions are designed and determine what research designs and evidentiary standards are justified. While the ISSCR acknowledges the need for regulatory flexibility and the existence in many countries of numerous regulatory pathways intended to accelerate clinical translation, all such pathways should require substantial evidence of safety and effectiveness before products are advertised to patients and delivered as a routine component of clinical practice.

Fourth, there is considerable interest at present in "real world evidence" and other research findings that are



not necessarily generated in the context of well-designed and rigorously conducted controlled clinical trials (Collins et al., 2020). In particular, in the stem cell space there is considerable support for the use of patient registries as an alternative to conducting randomized controlled trials. The revised ISSCR Guidelines acknowledge the historical and contemporary significance of patient registries. Registries of particular patient populations can, for example, be used to record and analyze important clinical data concerning the natural history and progression of diseases. Such data can in turn be used to facilitate the development of meaningful clinical endpoints, biomarkers, and outcome measures. Registries can also serve as crucial tools for tracking adverse events after regulatory bodies have approved a particular stem cell-based product or other cell-based intervention for routine clinical use. However, as important as such registries are, they should not be used as a substitute for well-designed and properly conducted randomized controlled trials that are intended to test the safety and efficacy of stem cell-, cell-, or gene-based interventions and determine whether their use is supported by substantial evidence of safety and efficacy. Furthermore, registries and databases of clinical trials should be confined to legitimate clinical trials and should not be co-opted as promotional tools by businesses selling unproven stem cell products administered on a pay-to-participate basis in poorly designed and inadequately conducted studies that fall outside the scope of credible clinical research capable of generating meaningful safety and efficacy data (Wagner et al., 2018).

Fifth, in the past the ISSCR has acknowledged that there may be circumstances in which medical innovation is warranted and unproven and unlicensed stem cell products can be administered to a patient

outside clinical studies. While the ISSCR acknowledges the historical importance of medical innovation in the development of new treatments, particularly novel surgical interventions, overly broad interpretations of what constitutes medical innovation can facilitate premature commercialization of stem cell-based interventions. Administration of novel stem cell-based interventions outside regulated clinical studies can also result in stem cell researchers or other parties engaging in clinical activities that do not comply with applicable regulatory requirements. Acknowledging the place of medical innovation in developing new therapies while also recognizing how this concept can be abused, the ISSCR's Guidelines narrow the medical innovation category to the following: cell-based products that have already been approved for a particular use and are being administered on an off-label basis; are minimally manipulated, homologous use cells, or tissues that do not pose substantial risks to recipients; or are unproven interventions provided to patients via expanded access regulatory pathways. In this revised formulation, medical innovation with cells and tissues remains permissible but is subject to restrictive provisions. These well-defined constraints are intended to minimize risks to patients, support the development of safety and efficacy data in well-designed and properly conducted clinical trials, require independent oversight, and reduce the likelihood that the concept of medical innovation is used in an attempt to justify the delivery of cell-based interventions that are not backed by substantial evidence of safety and efficacy.

Conclusion

The ISSCR's Guidelines for Stem Cell Research and Clinical Translation are intended to be responsive not just to developments in stem cell research

but also to changes in the broader social, ethical, and legal contexts in which stem cell research and clinical translation occurs. The Guidelines must therefore not remain static. Instead, to be relevant, responsive, and helpful, the ISSCR's Guidelines will continue to undergo revision and development. The current Guidelines reflect this commitment to articulating in a timely and responsive manner general norms and principles, scientific and ethical standards, and specific recommendations. In particular, they reflect the ISSCR's longstanding commitment to supporting the development of safe and efficacious stem cell-based interventions that, well-defined exceptions notwithstanding, are carefully tested in well-designed and rigorously conducted clinical trials and are subject to independent regulatory oversight before entering the marketplace. The ISSCR continues to promote efforts that advance the well-being and safety of patients and research subjects and opposes attempts to exploit for commercial gain the hope, suffering, and vulnerability of ill or injured persons (Kimmelman et al., 2016; Sugarman et al., 2018).

ACKNOWLEDGMENTS

The author wishes to thank Eric Anthony, Melissa Carpenter, and Robin Lovell-Badge for the thoughtful feedback they provided in response to an earlier version of the manuscript.

DECLARATION OF INTERESTS

L.T. is a member of the ISSCR as well as a member of the organization's Ethics Committee and Membership Committee. L.T. served as a member of Working Group Four as the Guidelines were revised and expanded. L.T. is also a member of other organizations supporting responsible evidence-based clinical translation of stem cell products. On a pro bono basis, L.T. has served and continues to serve as an expert witness in a civil lawsuit involving issues related to the subject matter of this paper.



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