# Co-opting of ClinicalTrials.gov by "patient-funded" cell-based studies for respiratory diseases

Darcy E. Wagner[1,2], Ph.D., Leigh Turner[3], Ph.D., Angela Panoskaltsis-Mortari[4], Ph.D., D(A.B.M.L.I.), Daniel J. Weiss[5], M.D., Ph.D., Laertis Ikonomou[6,7], Ph.D.

[1]Department of Experimental Medical Sciences, Wallenberg Center for Molecular Medicine, Lund University, Lund, Sweden, [2]Lund Stem Cell Center, Faculty of Medicine Faculty of Medicine, Lund University, Lund, Sweden, [3]Center for Bioethics, School of Public Health & College of Pharmacy, University of Minnesota, Minneapolis, MN, [4]Departments of Pediatrics and Medicine, University of Minnesota, Minneapolis, MN, [5]University of Vermont College of Medicine, Burlington, VT, [6]The Pulmonary Center, Boston University School of Medicine, Boston, MA, [7]Center for Regenerative Medicine (CReM) of Boston University and Boston Medical Center, Boston, MA

Correspondence and requests for reprints should be addressed to Laertis Ikonomou, Ph.D., Center for Regenerative Medicine (CReM), Boston University and Boston Medical Center, 670 Albany St., 2nd Floor, Boston, MA 02118, email:laertis@bu.edu, Phone: 617-638-4468

Keywords: ClinicalTrials.gov, Unproven "stem cell" interventions, Institutional Review Board, Lung disease, Pay-to-participate, Investigational New Drug, NIH.

Regenerative medicine approaches for the treatment and management of lung diseases hold great promise. There have been tremendous advances in lung stem cell biology and lung bioengineering during the last decade as well as the development of a large and growing literature demonstrating the efficacy of systemic or intratracheal administration of cells, including mesenchymal stromal cells (MSCs), macrophages, or endothelial progenitor cells (EPCs), in pre-clinical models of lung injuries and diseases. Despite these advances, the effectiveness of cell-based interventions for any respiratory disease has not yet been demonstrated in clinical studies. In stark contrast to this clinical reality, businesses advertising unproven and unlicensed “stem cell” interventions for lung diseases such as chronic obstructive pulmonary disease (COPD) and interstitial lung disease have proliferated.[1-3]

One of the markers of scientific legitimacy[4] such businesses use to promote their commercial activities and solicit prospective clients is the registration and listing of “patient-funded” studies on the National Institutes of Health (NIH)-administered website, ClinicalTrials.gov. At present, studies registered on ClinicalTrials.gov are not reviewed and screened in a rigorous and comprehensive manner. As a result, clinical trials that are well-designed and compliant with contemporary ethical, scientific, and regulatory standards are included in the registry and searchable database along with studies that do not comply with ethical and legal norms governing human subjects research. In particular, studies that charge participants $7,500 USD to $20,000 USD or more raise a number of ethical concerns[5] and can be found in the database. This comingling of credible, justifiable clinical trials with pay-to-participate studies of questionable scientific validity or oversight is confusing and misleading to prospective research participants. It also raises the specter

of ClinicalTrials.gov, a website designed to promote transparency and integrity in clinical research, being repurposed as a marketing platform by businesses selling unproven "stem cell" interventions.

Many such studies listed on clinicaltrials.gov have sought and received approval from commercial Institutional Review Boards (IRBs) of varying degrees of rigor. IRB approval has been obtained even when studies have not been reviewed and permitted to proceed by national regulatory bodies such as the U.S. Food and Drug Administration (FDA).[6] Some of the listed studies use terminology such as "stem cell treatments" or 'therapies' which suggests scientific validity. The use of this terminology can confuse or mislead study subjects and undermines their ability to make informed decisions about whether to participate in clinical research.[7] The deleterious consequences associated with allowing studies of questionable ethical, scientific, and legal standing into ClinicalTrials.gov are dramatically illustrated by the recent case of three patients diagnosed with age-related macular degeneration who sustained irreversible vision loss after receiving unproven and unlicensed adipose-derived stem cell products administered in a "pay-to-participate" study listed on ClinicalTrials.gov.[8]

The NIH has recently taken some meaningful steps to tighten the registration process and reporting requirements.[9] This is an encouraging development but more changes are needed. While we acknowledge that the NIH may not have the resources to appropriately evaluate and screen every study submitted to ClinicalTrials.gov for registration,[10] including 73 trials listed involving cell-based treatments for a range of lung diseases and related pulmonary critical illnesses as of May 7, 2018, we argue there is an urgent need to develop additional safeguards that improve transparency in order to protect prospective

study subjects from studies that fail to comply with basic standards for conducting clinical research. Studies which do not comply with basic ethical standards for human subjects research should not be registered on ClinicalTrials.gov.

We propose several safeguards that would help protect the integrity of ClinicalTrials.gov.

First, the process of identifying and reporting studies of questionable ethical, scientific, and regulatory standing to the NIH should be more straightforward.

Second, the regulatory status of cell-based products used in ClinicalTrials.gov-listed studies needs to be more easily identifiable by the inclusion of relevant information such as whether or not studies have been submitted for review to the FDA or other legitimate global regulatory organizations and permitted to proceed.

Third, streamlined and user-friendly processes for flagging problematic “pay-to-participate” studies on ClinicalTrials.gov should provide opportunities for addressing potential issues related to informed consent and IRB approval of unproven and unlicensed “stem cell” interventions. There should be the possibility of direct reporting of questionable instances of IRB approval or problematic informed consent issues to the FDA, to the federal Office for Human Research Protections (OHRP), and to state medical boards.

Fourth, sponsors should be required to provide Investigational New Drug (IND) application numbers during the registration process. Any study that is to take place in the United States and that lacks an IND number should not be posted without further review.

The latter proposed requirement is of particular importance in lung-related disease studies where, in one type of example, the administration of autologous adipose tissue-derived stromal vascular fraction (SVF) is commonly marketed by businesses as effective "stem cell treatments" provided in the context of "pay-to-participate" studies. According to the FDA, such uses of SVF in non-cosmetic applications require premarketing authorization by the FDA. Approval of biologics licenses for such stem cell-based products must be preceded by demonstration of safety and efficacy in well-controlled IND studies.[11]

Listing of non-FDA-reviewed and "pay-to-participate" lung-disease related studies on ClinicalTrials.gov compounds the problem of businesses selling unproven and unlicensed "stem cell" interventions by associating such commercial activities with the name and reputation of the NIH. Preserving the integrity of the registry, helping prospective study subjects identify clinical trials that comply with current ethical, scientific, and regulatory standards for human subjects research, and cautioning patients to be wary of unproven interventions that could cause medical harm and involve often substantial financial expenditures should be high priorities for the many stakeholders involved in lung regenerative medicine.

## References


1. Ikonomou L, Freishtat RJ, Wagner DE, Panoskaltsis-Mortari A, Weiss DJ. The Global Emergence of Unregulated Stem Cell Treatments for Respiratory Diseases Professional Societies Need to Act. *Ann Am Thorac Soc* 2016; **13**(8): 1205-7.
2. Berger I, Ahmad A, Bansal A, Kapoor T, Sipp D, Rasko JEJ. Global Distribution of Businesses Marketing Stem Cell-Based Interventions. *Cell Stem Cell* 2016; **19**(2): 158-62.
3. Turner L, Knoepfler P. Selling Stem Cells in the USA: Assessing the Direct-to-Consumer Industry. *Cell Stem Cell* 2016; **19**(2): 154-7.
4. Sipp D, Caulfield T, Kaye J, et al. Marketing of unproven stem cell-based interventions: A call to action. *Sci Transl Med* 2017; **9**(397): 5.
5. Emanuel EJ, Joffe S, Grady C, Wendler D, Persad G. Clinical research: Should patients pay to play? *Sci Transl Med* 2015; **7**(298): 4.
6. Turner L. ClinicalTrials.gov, stem cells and 'pay-to-participate' clinical studies. *Regen Med* 2017; **12**(6): 705-19.
7. Interlandi J. The Trouble With Stem Cell Therapy. January 11 2018. https://www.consumerreports.org/medical-treatments-procedures/trouble-with-stem-cell-therapy/ (accessed May 28 2018).
8. Kuriyan AE, Albini TA, Townsend JH, et al. Vision Loss after Intravitreal Injection of Autologous "Stem Cells" for AMD. *N Engl J Med* 2017; **376**(11): 1047-53.
9. Zarin DA, Tse T, Williams RJ, Carr S. Trial Reporting in ClinicalTrials.gov - The Final Rule. *N Engl J Med* 2016; **375**(20): 1998-2004.
10. ClinicalTrials.gov. Number of Registered Studies Over Time. March 2018. https://clinicaltrials.gov/ct2/resources/trends#RegisteredStudiesOverTime (accessed May 27 2018).
11. Marks P, Gottlieb S. Balancing Safety and Innovation for Cell-Based Regenerative Medicine. *N Engl J Med* 2018; **378**(10): 954-9.