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STEM CELLS TRANSLATIONAL MEDICINE

Ethical issues concerning a pay-to-participate stem cell study

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Abstract

In our critique of a pay-to-participate study, we address how the failure to disclose study-related payments appears to have violated *STEM CELLS Translational Medicine's* editorial policies concerning conflict-of-interest and financial disclosure. Our analysis also identifies broader ethical issues and scientific concerns related to pay-to-participate studies conducted by businesses with a record of selling purported stem cell treatments before determining whether the products they sell are safe and efficacious. Authors of peer-reviewed articles have a responsibility to comply with journal policies and disclose financial conflicts of interest to editors, reviewers, and readers. Authors should also disclose when stem cell interventions being tested in clinical trials have already been sold on a direct-to-consumer basis as "stem cell treatments" by authors' affiliate institutions. Financial conflicts of interest and other forms of possible bias must be disclosed to put clinical studies in context and facilitate the critical assessment of research methods, findings, and conclusions. The apparent failure to comply with journal editorial policies and disclose such financial conflicts warrants careful investigation.

KEYWORDS
clinical trials, ethics, mesenchymal stem cells (MSCs), stem cells, umbilical cord

1 | INTRODUCTION

There are currently no stem cell therapies for autism spectrum disorder (ASD) that are backed by convincing evidence of safety and efficacy generated in randomized controlled trials. Several unblinded, nonrandomized, and uncontrolled studies have found that the administration of stem cell products might benefit some persons with ASD.[1-5] However, these studies are preliminary in nature. Randomized controlled trials using stem cells as investigational products administered to persons with ASD have not demonstrated convincing evidence of efficacy.[6,7] There are no licensed stem cell therapies for ASD, and stem cell interventions are not part of the evidence-based standard of care for persons with ASD. Despite the lack of robust safety and efficacy data supporting the use of stem cell-based therapies in individuals with ASD, many parents pursue such interventions for their children with ASD.[8,9] The costs of these unproven interventions are typically not covered by health insurance. Families therefore sometimes engage in crowdfunding to pay for procedures that cost thousands of dollars.[10,11]

In a recent study we conducted of crowdfunding campaigns soliciting donations intended to fund access to purported stem cell interventions for neurological indications, we found that 23% of campaigns identifying a specific destination facility were for individuals seeking to have such procedures at the Stem Cell Institute (SCI), located in Panama City, Panama.[12] This facility particularly drew the interest of campaigns for people with ASD. Two thirds of all campaigns that were for persons with ASD and that named an intended facility specified the SCI as the destination site. Our findings suggest

that the SCI has a significant place within the global marketplace of businesses selling unproven stem cell interventions for neurological indications generally and for ASD specifically.

2 | PAY-TO-PARTICIPATE STUDY CONDUCTED AT THE SCI

Given the prominent place of the SCI in the global marketplace for unproven stem cell interventions, we are concerned about the publication in *STEM CELLS Translational Medicine* (*SCTM*) of a peer-reviewed article that describes a clinical study conducted at the SCI without disclosing that study subjects were charged as a criterion of inclusion. The authors also failed to disclose that the SCI has for more than a decade sold on a direct-to-consumer basis purported stem cell treatments for ASD and other diseases and injuries even though to date there is no convincing evidence from randomized controlled trials that the stem cell interventions this business markets are safe and efficacious in the treatment of ASD, cerebral palsy, spinal cord injuries, and other diseases and injuries. Such commercial activity should have been disclosed by the study authors.

The article, "Allogeneic Human Umbilical Cord Mesenchymal Stem Cells for the Treatment of Autism Spectrum Disorder in Children: Safety Profile and Effect on Cytokine Levels," was published in 2019.[13] The article reports findings from what the authors describe as a "phase I/II clinical trial" involving administration of expanded allogeneic human umbilical cord-derived mesenchymal stem cells to 20 children diagnosed with ASD. The children were administered four intravenous infusions of the investigational stem cell product every 12 weeks, commencing at week 1 and followed by weeks 13, 25, and 37. The study was an open-label, single-arm trial in which stem cells were administered to minors between the ages of 6 and 15 years. The average age of children in the study was 10.25 years.

SCI's practice of charging its clients to access unproven stem cell interventions extended to this study.[14] While not disclosed in the article, one inclusion criterion for participating in this study was being able to pay $7200 USD per child in addition to travel expenses.[15] This study therefore falls into the category of a patient-funded or pay-to-participate stem cell study.[16]

As prior scholarship on pay-to-participate studies notes, such studies often contain significant scientific limitations and undisclosed forms of bias that throw into question the credibility of reported findings, including claims about the purported safety and efficacy of the administered product.[17-20] Pay-to-participate studies commonly are not randomized, blinded, and controlled, include only those study subjects with the financial means to participate, and often are dependent on quality of life surveys or other instruments in which study subjects or observers offer subjective health assessments rather than using more objective forms of evaluation. In what follows, we focus upon one study published by a business that plays a prominent role in the global direct-to-consumer marketplace for unproven stem cell products. However, many of our concerns apply to other pay-to-participate studies conducted by business engaged in selling unproven stem cell products or other interventions that are unsupported by convincing evidence of safety and efficacy.

Significance statement

The present study describes important financial conflicts of interest that were not disclosed in an article published in *STEM CELLS Translational Medicine*. This article reinforces that such information needs to be provided to journal editors, reviewers, and readers. This information is important because the failure to provide it can help conceal significant biases from readers. The authors also argue for the importance of disclosing financial conflicts of interest that exist when studies are conducted at institutions already marketing and selling as "therapies" the very stem cell products being tested in clinical trials as investigational interventions.

3 | DOCUMENTING ADVERSE EVENTS

One problem with pay-to-participate studies, particularly when they are conducted by businesses already selling the very "stem cell therapies" they represent themselves as testing in clinical trials, is that the investigators can have a financial stake in bolstering their ongoing business operations. For example, such researchers can be biased toward finding that the stem cell interventions they are already advertising and administering are safe and efficacious.

In this study, 133 adverse events were observed during 296 infusions, but the researchers classified just 58 of them as related to the administration of stem cells. While this count might be accurate, the researchers do not explain how they made determinations of causality or why the other 75 reported adverse events were classified as "not related" or "not likely related" to the stem cell product and not further described or quantified. It is possible that financial interests—whether connected to payments as a criterion of study inclusion or to SCI's more general commercial interest in attracting customers for the purported stem cell treatments it sells—could have introduced bias into the process of detecting, classifying, and counting investigational product-related adverse events. Study authors with a financial relationship to companies that have already engaged for years in direct-to-consumer marketing and sale of putative stem cell treatments and have a financial interest in continuing to sell such products could suffer from bias that leads to underreporting of adverse events or misclassification of whether particular adverse events were attributable to study-related investigational stem cell products. Indeed, documenting serious adverse events or reporting absence of efficacy after clients have already been sold and provided such products could expose businesses to increased risk of civil litigation or regulatory action if former patients were injured, deceived, or otherwise harmed.

4 | PLACEBO RESPONSE AND PLACEBO AMPLIFICATION

Payments by the parents of study participants risk undermining the objectivity of the Autism Treatment Evaluation Checklist and Childhood Autism Rating Scale completed by the parents of participants in this study. One significant limitation with charging parents in this manner is that parents might have then found themselves financially, psychologically, and emotionally invested in the success of the putative "stem cell treatment" for which they had paid. The placebo response is a well-known problem that makes it challenging to determine whether interventions intended to treat symptoms associated with ASD truly are efficacious.[21-24] The amplification of the placebo response can occur when individuals have paid substantial fees for a purported treatment or were otherwise primed to identify benefits resulting from supposed therapies.[17,25,26]

If the process known as placebo amplification occurred in this study, parents might have been primed by the payment of $7200 per child and travel fees—payments that were a criterion for participating in the study—to be biased toward detecting a reduction in symptoms and an improvement in the communication skills and behavior of their children following administration of stem cells. The study does not acknowledge the possibility that claims by some parents that they detected reduced symptoms and behavioral improvements in their children might be attributable to the placebo response combined with placebo amplification connected to paying for their children to participate in the study. Having parents assess their children using these tools prompts concerns that the study's claim that some children reached a lower ASD symptom category as a result of being administered stem cells is attributable to placebo amplification. As these payments were not disclosed in the article, journal editors, reviewers, and readers were not provided with the information they needed to interpret possible bias in these results.

The authors claim the study's results "are indicative of potential therapeutic benefits" and provide "trends and signals that should be further explored in larger double-blind, placebo-controlled studies." To the contrary, the study results might be attributable to placebo amplification resulting from the undisclosed payments made by parents who subsequently completed the checklist and rating scale. Despite the absence of convincing evidence of efficacy, SCI continues to sell purported stem cell treatments for autism, cerebral palsy, and other diseases and injuries.[27] While our analysis focuses on this study, we are also concerned about how SCI is using this published peer-reviewed article to help legitimize the sale of unproven stem cell interventions.

5 | ADVERTISING CLAIMS AND INFORMED DECISION-MAKING

According to the article, "Written informed consent was obtained for all study participants and cord donors." Despite this claim, there is reason to question the general adequacy of information provided by the SCI to parents of children with ASD and to adults diagnosed with ASD. SCI has a lengthy history of advertising unproven stem cell interventions for ASD. It markets these procedures to prospective clients as "stem cell treatments" or "therapies." While the business provides caveats such as noting that "efficacy has not been proven" and the "treatments" it markets "have not been evaluated by the U.S. FDA and are not considered to be standard of care for any condition or disease," SCI also claims it can provide "stem cell therapy for autism."[28]

SCI notes that "The results of testimonials of people who appear on this website who have undergone stem cell treatment are not necessarily typical."[29] Nonetheless, SCI uses such testimonials to convey to prospective clients that its putative stem cell therapies can help adults and children with ASD.[30] Such testimonials appear intended to persuade parents that their children will exhibit fewer symptoms of ASD after being administered stem cells. We are concerned that the general marketing message promoted by SCI is one that overestimates the likelihood of benefits from the purported stem cell treatments, fails to acknowledge that the company lacks convincing evidence of safety and efficacy for the stem cell interventions it sells, and undermines informed decision-making. While we do not question that SCI obtained signed informed consent forms from parents for this study, we are concerned about the information SCI provided to study participants and to other customers who received the company's stem cell products outside clinical studies. In particular, we are concerned about how SCI's marketing claims could influence decision-making by the company's clients.

It is unclear why SCI conducted a preliminary clinical study while also selling putative stem cell treatments for ASD and numerous other indications before, during, and after the study was conducted. There is reason to question the accuracy of various representations SCI has made and continues to make about its putative stem cell treatments for ASD. The authors' claim that informed consent was obtained for the study fails to address or even acknowledge the more problematic features of SCI's marketing claims about providing stem cell therapy for ASD. Some of these troubling ethical issues might have surfaced in the article if the authors had disclosed that the study was conducted at a facility already selling purported stem cell treatments for ASD.

6 | *SCTM's* EDITORIAL POLICIES CONCERNING CONFLICT OF INTEREST AND FINANCIAL DISCLOSURE

Undisclosed financial conflicts of interest and other forms of hidden bias are serious issues in biomedical research and are not confined to "pay-to-participate" clinical studies. Acknowledging this point, conducting a clinical study in which payment is a criterion of inclusion and the researchers are connected to a business that benefits financially from selling an unproven stem cell intervention for ASD greatly increases the challenges associated with producing reliable and unbiased research findings and reporting them in a responsible and accurate manner.[31]

To evaluate financial conflicts of interest and related forms of bias that might influence clinical findings and their interpretation, editors, reviewers, and readers of scientific articles must be told when payment constitutes an inclusion criterion for participating in a study.[15,32] Investigators conducting studies in which stem cells are administered as investigational products to research participants should also disclose if they are or have engaged in selling as "stem cell treatments" the very interventions being tested within clinical studies for evidence of safety and efficacy. Such activity prompts questions about the scientific and ethical basis for advertising and administering stem cell products before convincing evidence of safety and efficacy exists.

The failure of the authors to disclose payments related to the inclusion of study participants in the clinical trial and the SCI's record of charging its clients for unproven stem cell interventions before, during, and after this study appears to have violated *SCTM's* editorial policies. Specifically, this policy requires authors to "disclose any financial relationship that is relevant to the work, and that might be perceived as a conflict of interest."[33] Moreover, authors have an obligation "to disclose any financial relationship that may present a potential conflict of interest in the communication of nonbiased scientific information." The journal's editorial policies add, "authors must also disclose funding sources for clinical trials, including patient-funded trials." As a matter of editorial policy, to "ensure full transparency of the peer-review and publication processes," the journal's editors, reviewers, and readers are supposed to be informed of "any financial relationships that may be pertinent to the article." The journal's editorial policies state that the failure to disclose all such financial relationships can, following investigation, lead to a finding of misconduct. Given that relevant financial conflicts-of-interest were not disclosed by the authors of this study, we believe this article failed to comply with the journal's editorial policies. The apparent failure to comply with journal editorial policies and disclose such financial conflicts warrants careful investigation.

7 | CONCLUSION

Our critical analysis is focused on one peer-reviewed study conducted by a business with a significant presence in the global direct-to-consumer marketplace for purported stem cell treatments. However, many of our concerns about this study apply to other peer-reviewed articles documenting findings from stem cell studies where payment is a condition of study inclusion, this information is not disclosed to journal readers, and authors also do not disclose that they have conducted their study at a business with a history of selling these products as therapies. Such publications and related failures to disclose financial conflicts-of-interest are likely to increase as clinics selling on a direct-to-consumer basis purported stem cell treatments or other unproven interventions publish pay-to-participate studies in an attempt to legitimize their commercial activities.[34] Organizations such as the International Society for Stem Cell Research are aware of this trend and identify payment-to-participate in research as among the "signs of a problematic stem cell-based clinical trial."[35] If payment to participate in research is a criterion for inclusion in a trial, that information needs to be disclosed to journal editors, reviewers, and readers. Likewise, these parties need to be informed if researchers are publishing findings concerning "investigational" stem cell products or other unproven products while also selling such interventions as "treatments." Individuals associated with businesses engaged in such activity know that articles published in academic journals can be used as influential "tokens of scientific legitimacy."[36] Such indications of apparent credibility can play an important role in persuading prospective clients to spend thousands or tens of thousands of dollars on stem cell products unsupported by convincing evidence of safety and efficacy.

CONFLICT OF INTEREST

The authors declared no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

L.T., J.S.: conception and design, critical analysis, manuscript writing, final approval of manuscript, other tasks related to preparing the article for submission.

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