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LETTER TO THE EDITOR

STEM CELLS TRANSLATIONAL MEDICINE

Addressing concerns regarding associated costs, transparency, and integrity of research in recent stem cell trial

We have read with significant concern that our paper[1] has been cited in Volume 10, Issue 6 (June 2021) in a manuscript titled "Ethical issues concerning a pay-to-participate stem cell study" authored by Turner and Snyder.[2] While we recognize and welcome the need for dialog and academic discussion in the field of regenerative medicine, particularly from a bioethical perspective, our study was not a pay-to-participate study. In fact, we went to great effort to ensure that the treatments were completely funded by the sponsor. In our diligent management of conflicts of interest and bioethics, we obtained the Institutional Review Board (IRB) advice to include in the informed consent and on ClinicalTrials.gov an estimate of out-of-pocket expenses the subject may incur for transportation, lodging, and meals, none of which are expenses of the treatment, but are expenses incurred by subjects in most trials. It is regrettable that our study was misrepresented by the authors, especially since we clarified this issue during the peer-review process with this journal.

During the peer-review process of this journal (answer to Q15 of the Lead Reviewer in the first revision, along with a link to clinicaltrials.gov[3]) and, later on, in a communication with the Editor dated February 16, 2021, we clarified that our study treatments were not paid for by participants. Our answer has not changed: the subjects of this trial did not pay for treatment, as is clearly stated in our protocol. Items not paid for by the participants include prestudy exams, drugs, delivery of drugs, medical services for treatment or follow-up, statistical analysis, study documentation, utilities or rent, employees and support personnel for the clinic during the trial, recruitment, data management, clinic facility fees, physician time, medical staff, clinical trial insurance cost, 24/7 medical assistance, subject coordinators, or the independent CRO services in conducting the trial. These costs were entirely covered by the study sponsor, not in any way by the subjects.

The U.S. $7200 that appears on clinicaltrials.gov[3] was an amount estimated to cover incidental, nontreatment-related costs such as transportation, lodging, meals, and other logistics expenses (maximum U.S. $1800 per visit $\times$ 4 visits $=$ $7200). These expenses were incurred by participants from third parties, not the sponsor; and they were in no way expenses of conducting the study or administering the therapy, as mentioned above. This separation of logistic expenses from study expenses was clearly established in the protocol. It was communicated to the guardians of the participants during recruitment to fully inform them and make them aware that they would incur those expenses.

It is unreasonable to consider payment of incidental expenses by participants in a clinical study as a breach of scientific integrity. In virtually every study conducted, participants incur some expenses, like those for transportation to the study site or food on the way to or from treatment, phone expenses, loss of wages, and the list goes on. If participant payment of these incidental expenses adversely affects the integrity of the science of a study, then most all of the peer-reviewed literature on medical research in even our most prestigious journals would be discredited. How does payment of these incidental expenses adversely affect the scientific integrity of the study? Bioethics call for management and transparency of any potential or perceived conflicts of interest to ensure the scientific integrity of the study.

For transparency, this cost for other expenses was always publicly available on clinicaltrials.gov.[3] We indicated the clinicaltrials.gov identifier in the manuscript, and we linked to it in the cover letter of the first round of revisions, which satisfied the reviewers. We have been always transparent about this information. We hope this sufficiently clarifies that subjects did not have to pay to "participate" in this trial neither from our perspective, nor from that described in another article[4] in the same issue as Turner and Snyder's.

Regarding any potential conflicts of interest, these were clearly indicated in the appropriate section of the article[1]: "N.H.R. and J.P.R. declared leadership position, patent holder, and shareholders of MediStem Panama and the Stem Cell Institute. M.L.H. declared research funding as subinvestigator for Stem Cell Institute. I.M., N.A. declared leadership position with MediStem Panama. G.F., C.L. declared leadership position with Stem Cell Institute. M.M. declared leadership position and stock ownership with MediStem Panama. N.N. declared research funding from MediStem Panama." This information is available along with the article and was in no way withheld during the peer-review stage or after publication.

To manage conflicts of interest, our Clinical Trials Department is staffed by researchers who are not involved with commercial activities. All meetings for the preparation of this article were approached

See related Editor's note

with utmost objectivity, from a research perspective, and with no "direct-to-consumer marketing and sale of putative stem cell treatments and (…) a financial interest in continuing to sell such products"[2] ulterior motives. Moreover, there was no bias in classifying adverse events as "related to treatment"—some of the events recorded (1) are as benign as ant or mosquito bites and rashes, (2) respond to clinical issues noted prior to treatment, or (3) were deemed to be unrelated to treatment by licensed medical professionals. We stand by the medical integrity of our researchers and the research in this study. At the request of one of the reviewers (Q11 by the Lead Reviewer), we did include all events deemed related to the study. The peer-reviewing process for this article was exhaustive and included numerous clarifications that were invaluable in transparently, concisely, and clearly communicating the methods, results, and conclusions of this study.

Finally, our study conclusions were well supported by the data. We have maintained a cautious tone in reporting all findings of this study and have called for larger studies to be conducted with this approach ("Although encouraging, the results of this study should therefore be taken as indicative of trends and signals **that should be further explored** in larger, double-blind, placebo-controlled studies."—bolded for emphasis)[1] As stated in the conclusions,[1] the administration of umbilical cord-derived mesenchymal stem cells was well tolerated with no serious adverse events in a reduced sample size (only 10 completed the full study) of young patients with ASD, of which a percentage showed some improvement signals in cytokine levels and in the Childhood Autism Rating Scale (CARS) and Autism Treatment Evaluation Checklist (ATEC) scores. We have upheld scientific and medical professionalism in acknowledging the limitations of this study in the article, particularly highlighting the involvement of the parents in assessing any amelioration, and also noting the small sample size which calls for caution when approaching statistical significance issues.[1]

Our aim with this article was to evaluate the safety of umbilical cord-derived mesenchymal stem cells (UC-MSC) administration with the purpose of contributing to the many ongoing clinical studies of MSC administration worldwide. Our ultimate purpose is to see better funded, better designed, larger, placebo-controlled trials utilizing UC-MSCs, thereby allowing elucidation of their potential mechanisms of action.

We stand firm that our study was conducted with scientific integrity that transparency and potential conflicts of interest were properly managed with independent oversight by those without conflict of interest that the methods and results support the limited conclusions, and that our article contributes to the corpus of MSC research and to the still unresolved biomolecular etiology of autism spectrum disorder. We remain committed to scientific pursuit of potential novel therapies for the many children who suffer from this debilitating disorder. We have been committed to transparency and academic discussion from the start of the submission process of this article, and we hope this letter is conducive to a cordial, fact-based debate between interested parties.

CONFLICT OF INTEREST

N.H.R. declared a leadership position and is a shareholder in MediStem Panama & Stem Cell Institute. J.P.R. declared a leadership position and is a patent holder in MediStem Panama & Stem Cell Institute.

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