## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Allogeneic human umbilical cord-derived mesenchymal stem/stromal cells for chronic obstructive pulmonary disease (COPD): study protocol for a matched case-control, phase I/II trial |
| **AUTHORS** | Hoang, Duc M.; Nguyen, Kien T.; Nguyen, Anh H.; Nguyen, Bach N.; Nguyen, Liem |

## VERSION 1 – REVIEW

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| **REVIEWER** | Weiss, Daniel<br>University of Vermont |
| **REVIEW RETURNED** | 26-Dec-2020 |

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| **GENERAL COMMENTS** | This is a delineation of a phase 1/2 investigation assessing safety and efficacy of systemic administration of human umbilical cord blood-derived MSCs in patients with moderate-severe COPD. The trial is generally well presented and the manuscript well written. However, there are several issues for the authors to consider.<br><br>1. Perhaps I'm not understanding but will the MSCs to be administered all come from the same UC isolate? If not, is there to be a comparison or otherwise matching based on the MSC behaviors defined: expansion, differentiation, potency.<br><br>2. There is extended discussion about the relative merits of MSCs derived from different sources with the authors claiming that the UC MSCs are best situated for this study. While there is certainly merit in the ease of collecting umbilical cords compared to invasive procedures required for bone marrow or adipose sources, how robust are the other merits. MSCs from all sources can differentiate, be expanded in culture adequately for the relative low passage number that will be utilized in clinical studies (generally < passage 5-6), and have paracrine effects. It would seem that the more important information is whether MSCs from different sources behave differently or have different efficacies in relevant pre-clinical models of the disease being investigated, in this case COPD. Can the authors better clarify how the pre-clinical studies of MSCs inform this question.<br><br>3. In parallel, MSCs can do different things in different disease models, including different lung injury models. As such, referring to MSC effects in models of acute lung injury/ARDS are not necessarily directly relevant to potential use in COPD. To this end, what do the authors speculate as to potential mechanisms of MSC actions, specific for COPD.<br><br>4. To this end, while the lymphocyte proliferation assay is widely used as a marker of MSC potency, is this relevant for COPD? |

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| | 5. While there is reasonable rationale presented for the MSC dose to be utilized, the rationale for the dosing interval is less clear. Can the authors clarify this better.<br><br>6. There is good discussion about the various issues that can potentially affect MSC efficacy including use of continuously cultured vs freshly thawed cells. In their initial study (ref 18), frozen UC MSCs were thawed and cultured for 72 hours prior to administration, yet in the current investigation cells will be administered directly after thawing. Can the authors clarify why this approach is being utilized compared to their previous approach.<br><br>7. The endpoint measures are appropriate for the longer term follow-up periods delineated. However, there is no discussion or clarification of safety monitoring during the actual infusion period. Even though the previous clinical investigations in COPD patients have not demonstrated infusional toxicities or adverse events, it is important to continue to assess this possibility.<br><br>8. A small clarification: at different points in the manuscript, the authors have used phrases such as, “A large body of pre-clinical and clinical studies supports the safety and efficacy of MSC in the treatment of lung injuries, including COPD”. This is not quite accurate as, despite evidence of efficacy in pre-clinical models, no clinical studies to date have demonstrated efficacy in COPD or any other lung disease. This should be better clarified.<br><br>9. In the listing of strengths and limitations, it’s not clear how potential treatment effectiveness will be linked with stem cell phenotype analysis. There is mention in the secondary outcomes section of assessing circulating inflammatory mediators and also of characterizing MSC behaviors including metabolic evaluation, immunoregulatory assessments, and cytokine secretion. More details on all of this would be informative, perhaps in an additional table.<br><br>10. Despite the power analysis presented, based on a 60% change in mMRC outcome as delineated in the previous phase 1 trial, 20 patients in each group seems small, particularly for functional outcomes. Most trials of new potential COPD therapeutics require many more patients in order to have adequate power to discern any potential statistically significant difference, particularly in lung functions. For example, the Osiris trial (ref 15) was underpowered for detecting significant differences in lung functions even though there were approximately 30 patients in each cohort. Can the authors better justify their power analysis.<br><br>11. For clarification: reference 16 was not a trial of MSCs for COPD, rather the specific target was inflammation related to endobronchial valve placement.<br><br>12. In the secondary outcomes: how is “general self-efficacy” to be determined? |

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| **REVIEWER** | Stessuk, Talita<br>Sao Paulo State University Julio de Mesquita Filho - Assis Campus |
| **REVIEW RETURNED** | 29-Dec-2020 |

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| **GENERAL COMMENTS** | This protocol provides the first steps to address an interesting question: the safety and efficacy of allogeneic umbilical cord-derived mesenchymal stromal/stem cells (UC-MSCs) as an adjuvant intervention in combination with standard treatment in patients with advanced COPD. The protocol describes an ongoing matched case-control phase I-II trial which has the potential of, to a certain extent, reducing confounding variables such as stage of COPD, age and gender in the sampling design.<br><br>This study is technically sound and concisely presented. The research protocol has potential, but important clarifications and suggestions shall be considered as explained bellow.<br><br>Methods and analysis<br>Study objectives, page 5, lines 35-36: The authors state "There are two specific objectives:" while they list 3 specific objectives. Please clarify whether there are 2 or 3 specific objectives. In addition, it is not clear how the authors intend to investigate the therapeutic mechanism of UC-MSCs in the treatment of COPD. Please provide clarification on the third specific objective in the methods section.<br><br>Recruitment, page 7, lines 24-25: There is no informed consent form in the appendices. Please explain why such informed consent model was not attached to the manuscript.<br><br>Intervention, page 8, lines 16-17: "A single umbilical cord (UC) sample will obtained from healthy women". Please adjust the conjugation in "will obtained". In addition, this section requires few clarifications. First, it is not clear how many samples (donors) will be used to isolate UC-MSCs. Second, It is also not clear if the cells will be pooled. If this is not the case, please clarify if one patient will receive UC-MSCs from one single umbilical cord in both interventions. Third, please provide the reference which supports the isolation and culture of UC-MSCs (lines 24-25).<br><br>Statistical analysis strategy: Please provide clarification on matched analysis and the interpretation of confounding variables (stage of COPD, age and gender). Please clearly state whether conditional logistic regression models are. Going to be used for that benefit. |

## VERSION 1 – AUTHOR RESPONSE

**Reviewers' comments:**

**Reviewer #1:**

**General comments:** This is a delineation of a phase 1/2 investigation assessing safety and efficacy of systemic administration of human umbilical cord blood-derived MSCs in patients with moderate-severe COPD. The trial is generally well presented and the manuscript well written. However, there are several issues for the authors to consider.

- **Author Response:** We thank you for these comments.

**Specific comments:**

1. Perhaps I'm not understanding but will the MSCs to be administered all come from the same UC isolate? If not, is there to be a comparison or otherwise matching based on the MSC behaviors defined: expansion, differentiation, potency.
   - **Author Response:** We think the reviewer is referring to our statement on Intervention section (page 8, line 8 to 26). We confirm that the MSCs to be administered all come from a single UC sample to eliminate the biological variations of MSC product as reviewer's concern. To clarify, we altered the text on Intervention section (on Page 8, line 9 to 19) as follow:

     **"**Umbilical cord (UC) samples will be obtained from healthy women with an uncomplicated, at term pregnancy who underwent serological testing, including tests for HIV, cytomegalovirus (CMV), Epstein-Barr virus (EBV), hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), syphilis, and chlamydia, at 38 weeks of pregnancy. The UC tissues will be collected at delivery and transferred to the Stem Cell Core Facility at the Vinmec Research Institute of Stem Cell and Gene Technology under ISO 14644-1 (certification number: CR61119-1). To generate a UC-MSC line for the current study, a single eligible UC tissue will be processed, isolated and cultured under xeno-free and serum-free conditions as previously described".

2. There is extended discussion about the relative merits of MSCs derived from different sources with the authors claiming that the UC MSCs are best situated for this study. While there is certainly merit in the ease of collecting umbilical cords compared to invasive procedures required for bone marrow or adipose sources, how robust are the other merits. MSCs from all sources can differentiate, be expanded in culture adequately for the relative low passage number that will be utilized in clinical studies (generally < passage 5-6), and have paracrine effects. It would seem that the more important information is whether MSCs from different sources behave differently or have different efficacies in relevant pre-clinical models of the disease being investigated, in this case COPD. Can the authors better clarify how the pre-clinical studies of MSCs inform this question?
   - **Author Response:** In both preclinical models of COPD and clinical trials, MSCs regardless of their sources exhibit their therapeutic potential via either anti-inflammatory paracrine actions, reducing the rate of pulmonary fibrosis and/or lung recovery. In rodent models, studies using bone marrow-derived MSCs (BM-MSCs) or adipose-derived MSCs (AD-MSCs) have demonstrated that these cells administered via intravenous injection or intra-tracheal instillation were safe and effective in attenuating airway injury and enhance the recovery of lung functions via reducing airway inflammation and apoptosis (1). In mice model, administration of UC-MSCs (from Wharton's Jelly) significantly improved the pulmonary function and regeneration in COPD-induced mice compared to the sham group (2). To date, no comparative study is conducted to address the differences in efficacy introduce by MSCs from different sources. In our previous study, we demonstrated that

MSCs from perinatal and adult sources behaved differently even when they were cultured under a standardize culture platform (xeno-free and serum-free) (3). Therefore, although it seems that MSCs derived from different sources might show similar effects on COPD-induced animal models, we believe that the source of MSCs might play a role in the level of the therapy effectiveness and their mechanism of action might also different, especially when they are exposed to COPD-related microenvironment.

3. In parallel, MSCs can do different things in different disease models, including different lung injury models. As such, referring to MSC effects in models of acute lung injury/ARDS are not necessarily directly relevant to potential use in COPD. To this end, what do the authors speculate as to potential mechanisms of MSC actions, specific for COPD.
    - **Author Response:** We speculate the potential mechanism of MSC actions for COPD including:
        - Reduction of inflammatory reactions at injured airway via either paracrine effects (secretion of wide range of growth factors, cytokines and exosomes from UC-MSCs in response to the stimuli at injured sites) or cell-to-cell contact by interaction with immune cells.
        - Reduction of pulmonary fibrosis and airway thickening process post-administration.
        - Improve parenchymal repair by secretion of keratinocyte growth factor, hepatocyte growth factor, and epidermal growth factor.
4. To this end, while the lymphocyte proliferation assay is widely used as a marker of MSC potency, is this relevant for COPD?
    - **Author Response:** one of the mechanisms by which MSCs reducing pulmonary inflammation is via cell-to-cell contact with the immune cells. Hence, in this current study, we will design an experiment that co-cultures COPD patient's lymphocytes (before and after UC-MSCs administration at different timepoints) with UC-MSCs to evaluate the potential effect of UC-MSCs on patient's lymphocytes compare to that of healthy donors. Hence, this experiment is not only evaluating the UC-MSC potency but also reveal the potential mechanism of MSC actions in COPD patients. We expect the UC-MSCs would inhibit the proliferation of COPD patient's lymphocytes in a similar manner to that of healthy donor. The culture media of UC-MSC alone, lymphocyte alone, and co-culture of UC-MSCs and lymphocyte will be subjected to cytokines analysis of inflammatory factors such as IL-1β, TNF-α, IL-4, IL-8, IL-10, etc. to identify the release of soluble mediators from UC-MSCs that might involve in reducing lung inflammation.
5. While there is reasonable rationale presented for the MSC dose to be utilized, the rationale for the dosing interval is less clear. Can the authors clarify this better?
    - **Author Response:** We would like to thank the reviewer for the suggestion. We added a short discussion that explained the rationale for dosing interval on page 12 (line 19 to 26) as follow:
        - **"**In pre-clinical models of elastase-induced emphysema, two doses of MSCs improved anti-inflammatory regulation and lung recover compared to a single dose of MSCs (4).

In clinical trial using BM-MSCs, COPD patients received four infusions showed a reduction in circulating C-reactive protein and in combination with lung volume reduction strategy, two infusions were enough to increase the expression of CD31, an indication of microvascular endothelial cell response (5, 6). Moreover, the effects of autologous MSC administration were reported to be relatively narrow because it was reported the positive effects in patients with type 2 diabetes were observed as early as 1 month post-administration of MSCs and started to diminish after three to six months post-administration (7, 8). Hence, in this current study, we will perform two doses of UC-MSCs with a 3-month intervening interval."

6. There is good discussion about the various issues that can potentially affect MSC efficacy including use of continuously cultured vs freshly thawed cells. In their initial study (ref 18), frozen UC MSCs were thawed and cultured for 72 hours prior to administration, yet in the current investigation cells will be administered directly after thawing. Can the authors clarify why this approach is being utilized compared to their previous approach?
    - **Author Response:** We would like to confirm that the study (ref 18) was conducted by another research group from Vietnam, which is not our Vinmec Group. In our institute, we have done the administration of fresh UC-MSCs in treatment of bronchopulmonary dysplasia in preterm children – a study that we've also recently published (9). In the current study, we use UC-MSCs as an "off-the-shelf" product for administration, providing flexibility in patient management and standardized products for all treated patients, allowing more accuracy in evaluation and reducing confounding factors from biological products (listed on page 11, line 30 – 31).
7. The endpoint measures are appropriate for the longer term follow-up periods delineated. However, there is no discussion or clarification of safety monitoring during the actual infusion period. Even though the previous clinical investigations in COPD patients have not demonstrated infusional toxicities or adverse events, it is important to continue to assess this possibility.
    - **Author Response:** We would like to thank the reviewer for the suggestion. As we have listed out the potential adverse event (AEs – Page 9, line 4 – 15) and how we are going to monitor the safety outcome of the study (page 9, line 17 to 29). Moreover, we also added a short discussion of the safety in the Discussion (page 11, line 16 – 22) as follow:
        - "Several clinical trials have been conducted in COPD. Most of these studies were phase 1 safety trials, which uniformly reported no obvious adverse events and serious adverse events as well as no evidence of infusional toxicities during the follow-up period (6). However, the effectiveness of MSC therapy showed differences among various clinical trials, and a small number of trials have revealed no significant changes in lung function and fibrosis postadministration compared with baseline levels (10). Therefore, it is

important to comprehensively analyze the factors that directly contribute to treatment safety and efficacy."

8. A small clarification: at different points in the manuscript, the authors have used phrases such as, "A large body of pre-clinical and clinical studies supports the safety and efficacy of MSC in the treatment of lung injuries, including COPD". This is not quite accurate as, despite evidence of efficacy in pre-clinical models, no clinical studies to date have demonstrated efficacy in COPD or any other lung disease. This should be better clarified.
    - **Author Response:** We would like to thank the reviewer for the suggestion. We have altered the text in the Abstract (page 2, line 4-5) as follow: "A large body of preclinical and clinical studies supports the safety of mesenchymal stem/stromal cells (MSCs) in the treatment of lung injury, including COPD". We also emphasized in throughout the manuscripts that the study is designed to evaluate the safety as primary endpoint and potential efficacy as secondary endpoint.
9. In the listing of strengths and limitations, it's not clear how potential treatment effectiveness will be linked with stem cell phenotype analysis. There is mention in the secondary outcomes section of assessing circulating inflammatory mediators and also of characterizing MSC behaviors including metabolic evaluation, immunoregulatory assessments, and cytokine secretion. More details on all of this would be informative, perhaps in an additional table.
    - **Author Response:** Thank you for pointing this out. We added a new table in the revised manuscripts to provide more information (Table 4).
10. Despite the power analysis presented, based on a 60% change in mMRC outcome as delineated in the previous phase 1 trial, 20 patients in each group seems small, particularly for functional outcomes. Most trials of new potential COPD therapeutics require many more patients in order to have adequate power to discern any potential statistically significant difference, particularly in lung functions. For example, the Osiris trial (ref 15) was underpowered for detecting significant differences in lung functions even though there were approximately 30 patients in each cohort. Can the authors better justify their power analysis.
    - **Author Response:** Thank you for pointing this out. This is our mistake in the main outcome study which based on $FEV_1$ but not mMRC. Therefore, we corrected the sample size calculation as follows: "As a previous study indicated that the $FEV_1$ (%) of COPD patients was reduced to 35.4±7.1% (6% reduction) after 6 months post-administration, we set this indicator at 18% reduction after 12 months post-administration to calculate the minimum sample size for the proposed study(11, 12). According to the continuous endpoint of two independent sample studies(13), we assumed α was 0.05 and type-II error β was 0.2; thus, the smallest sample size was 40 patients. The calculated sample size was 20 for each group".
        - In addition, our study is phase ½ clinical trial, which focuses on the safety (primary endpoint) and potential efficacy (Secondary endpoint). Therefore, we aim to minimize the sample size at this phase to monitor carefully and precisely the potential AEs and SAEs could occur during the course of the

study. Once we finish this trial, the future trial would be phase 2b with larger cohort and stronger statistical power.

11. For clarification: reference 16 was not a trial of MSCs for COPD, rather the specific target was inflammation related to endobronchial valve placement.
    - **Author Response:** Thank you for pointing this out. According to the report, reference 16 demonstrated that the combined use of one-way endobronchial valves and MSCs appears to be safe in patients with severe COPD and suggested that MSC therapy could be used as concomitant therapy. Therefore, we believed that this could be considered as a trial of MSC for COPD.
12. In the secondary outcomes: how is “general self-efficacy” to be determined?
    - **Author Response:** We are using the COPD Self-efficacy scale for general self-efficacy, which was previously published (14).

**Reviewer #2:**

**Major comments:**

This protocol provides the first steps to address an interesting question: the safety and efficacy of allogeneic umbilical cord-derived mesenchymal stromal/stem cells (UC-MSCs) as an adjuvant intervention in combination with standard treatment in patients with advanced COPD. The protocol describes an ongoing matched case-control phase I-II trial which has the potential of, to a certain extent, reducing confounding variables such as stage of COPD, age and gender in the sampling design.

- **Author Response:** We thank you for these comments.

Methods and analysis:

Study objectives, page 5, lines 35-36: The authors state “There are two specific objectives:” while they list 3 specific objectives. Please clarify whether there are 2 or 3 specific objectives. In addition, it is not clear how the authors intend to investigate the therapeutic mechanism of UC-MSCs in the treatment of COPD. Please provide clarification on the third specific objective in the methods section.

- **Author Response:** Thank you for pointing this out. We corrected the typo on page 5 line 22 to “three specific objective”. We also add a table 4 on Page 10 line 6 to clarify the experiments related to the third specific objective and explain the expected outcomes of each experiments toward the aim.

Recruitment, page 7, lines 24-25: There is no informed consent form in the appendices. Please explain why such informed consent model was not attached to the manuscrip***t***.

- **Author Response:** Thank you for pointing this out. We have added the English version of informed consent to the revised manuscript. We forgot to add the informed consent on the first submission and we apologized for this inconvenient.

Intervention, page 8, lines 16-17: “A single umbilical cord (UC) sample will obtained from healthy women”. Please adjust the conjugation in “will obtained”. In addition, this section requires few clarifications. First, it is not clear how many samples (donors) will be used to isolate UC-MSCs. Second, It is also not clear if the cells will be pooled. If this is not the case, please clarify if one patient will receive UC-MSCs from one single umbilical cord in both interventions. Third, please provide the reference which supports the isolation and culture of UC-MSCs (lines 24-25***)***.

- **Author Response:** Thank you for pointing this out. We confirm that the MSCs to be administered all come from a single UC sample to eliminate the biological variations of MSC product as reviewer’s concern. We also added the ref for the xeno-free and serum-free culture conditions, which was our previous work to establish a standardized culture platform for AD, BM, and UC-MSCs. In this work, we collected 30 UC samples to create the bank that could be used for clinical applications and the line that are going to be used in this project is obtained from this bank. We have revised and structured the first paragraph of Intervention section (on Page 8, line 9 to 19) as follows:
    - **“**30 Umbilical cord (UC) samples were obtained from healthy women with an uncomplicated, at term pregnancy who underwent serological testing, including tests for HIV, cytomegalovirus (CMV), Epstein-Barr virus (EBV), hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), syphilis, and chlamydia, at 38 weeks of pregnancy , as shown in previous study (15). The UC tissues were collected at delivery and transferred to the Stem Cell Core Facility at the Vinmec Research Institute of Stem Cell and Gene Technology under ISO 14644-1 (certification number: CR61119-1). To generate a UC-MSC line for the current study, a single eligible UC tissue will be processed, isolated and cultured under xeno-free and serum-free conditions as previously described (15). UC-MSCs will be expanded under these conditions to passage 5 (P5) and cryopreserved in the serum- and xeno-free defined reagent CryoStore® CS10 (Stem Cell Technology, Canada) in liquid nitrogen (gas phase) in an automated Brooks System (Brooks Life Science, USA) for long-term storage. The releasing criteria for UC-MSC products are shown in Table 3”.

Statistical analysis strategy: Please provide clarification on matched analysis and the interpretation of confounding variables (stage of COPD, age and gender). Please clearly state whether conditional logistic regression models are. Going to be used for that benefit.

- **Author Response:** Our matched analysis will be followed the previously described studies (16, 17). In brief, we could perform a matched analysis (retaining the pair matching of one control for each case) using conditional logistic regression (equivalent to the Mantel-Hansel method). Our analysis will start first by using the Mantel-Hansel method to obtain preliminary crude effect estimates and effect estimates adjusted for each confounder separately. The cross-tabulations used for stratification in this technique allow us to observe the overall

important relationships and interaction that are present and to detect errors and inconsistencies in the data set that might not otherwise be evident. In the second stage, we will apply the conditional logistic regression models to estimate odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for main outcome values that are equivalent UC-MSC group and control group. We also considered the following covariates for inclusion in the final model: gender, age, stage of COPD to adjust simultaneously for confounders.

**References:**


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16. de Graaf MA, Jager KJ, Zoccali C, Dekker FW. Matching, an appealing method to avoid confounding? Nephron Clin Pract. 2011;118(4):c315-8.
17. Pearce N. Analysis of matched case-control studies. BMJ. 2016;352:i969.

**VERSION 2 – REVIEW**

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| **REVIEWER** | Weiss, Daniel<br>University of Vermont |
| **REVIEW RETURNED** | 07-Mar-2021 |

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| **GENERAL COMMENTS** | The authors have responded well to the reviewer comments and the manuscript is correspondingly improved. There remain two points for the authors to consider.<br><br>1. The response to reviewer comments concerning selection of umbilical cord-derived MSCs vs those obtained from other sources should be incorporated into the discussion. Same with the response on the rationale to perform lymphocyte assays and the mechanisms by which the authors think MSC administration will improve COPD.<br><br>2. The authors have not fully answered the question on any potential infusional toxicities. The table on timing of outcome measures does not include information on how the patients will be monitored during the actual infusion: continuous heart rate, blood pressure, arterial oxygenation (pulse oximetry) monitoring, etc. Despite the track record of safety in other investigations of MSC infusions, it is important to understand and communicate that these measures will be undertaken for safety monitoring. |

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| **REVIEWER** | Stessuk, Talita<br>Sao Paulo State University Julio de Mesquita Filho - Assis Campus |
| **REVIEW RETURNED** | 13-Mar-2021 |

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| **GENERAL COMMENTS** | The authors have properly addressed the main concerns and corrections in the manuscript. In addition, an interesting overview on experiments to evaluate potential therapeutic mechanisms of UC-MSCs was included to clarify their investigative strategy. |

**VERSION 2 – AUTHOR RESPONSE**

**Reviewers' comments:**

**Reviewer #1:**

**Specific comments:**

13. The response to reviewer comments concerning selection of umbilical cord-derived MSCs vs those obtained from other sources should be incorporated into the discussion. Same with the response on the rationale to perform lymphocyte assays and the mechanisms by which the authors think MSC administration will improve COPD.
    - **Author Response:** we have incorporated the response to reviewer comments to the discussion as the reviewer suggested on Page 12 (Line 12 to 35) and page 13 (line 1 and 2).

14. The authors have not fully answered the question on any potential infusional toxicities. The table on timing of outcome measures does not include information on how the patients will be monitored during the actual infusion: continuous heart rate, blood pressure, arterial oxygenation (pulse oximetry) monitoring, etc. Despite the track record of safety in other investigations of MSC infusions, it is important to understand and communicate that these measures will be undertaken for safety monitoring.
    - **Author Response:** We are totally agreed that safety monitoring of potential infusional toxicity is important part of the study. We have mentioned the measurements of heart rate, blood pressure, arterial oxygenation, etc. on Outcome Evaluation Section, Page 9 (line 22 to 25). We also added the D-dimer and thrombotic analysis to prevent blood clot and thrombotic events post-administration as potential risk. On the Table 2, vital signs and physical examination are also performed include body temperature, blood pressure, heart rate, respiratory rate, oxygen saturation, and patient body weight. We also added D-dimer in the Hematological analysis.