Author’s response to reviews

Title: Immersive virtual reality as analgesia for women during hysterosalpingography: study protocol for a randomized controlled trial

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Dear Editors and Reviewers,

Thank you for your kindness reviewing and giving valuable comments concerning our manuscript entitled “Immersive virtual reality as analgesia for women during hysterosalpingography: study protocol for a randomized controlled trial” (TRLS-D-19-00783). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. Revised portion are marked in red in the text. The main corrections in the paper and the responds to the reviewer’s comments are listed as following:

Yours sincerely,
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Reviewer #1

1. Thank you for providing further details of the associated funding for this work. Unfortunately there remains a lack of clarity with regards the funding and the link to this work. As a result, we must request that the reference to funding be removed from this submission, and so this treated as an 'unfunded' study. Please could you remove funding references accordingly.
Response: Thank you for your suggestion. We are sorry for the funding is not following the specified standards, we have removed funding references from this submission.

2. There are some typographical and grammatical errors throughout the manuscript e.g. Abstract - Background - Sentence 3 'AS' rather than 'As'; Background - Sentence 2 'stage' perhaps should be 'age'. A full proof reading of the manuscript is recommended to resolve these issues and increase readability.
Response: Thank you. We have taken every word of you. We have corrected those two words, and the manuscript has been polished thoroughly by Dr. Bo (an English teacher).

3. Please ensure acronyms are spelled out in full when first used in the main body of the manuscript. For example Background Sentence 4 commences with 'HSG' which has not previously been detailed in the main body of the manuscript.
Response: Pardon me for my carelessness. I have checked every acronym in the main body of the manuscript to ensure they are spelled out in full when first used.

4. Background - Paragraph 1 - Is there a reference to support the statement made in sentence 1?
Response: Sorry for my carelessness. There is a reference to support the statement made in sentence 1 and I have supplemented the reference into this submission.

5. Background - Paragraph 2 - You mention that the uncomfortable experience can lead to poor coordination. It wasn't clear who or what this was referring to - is this coordination of the patient or clinician, how is coordination affected.
Response: Sorry for making such an ambiguity. Here poor coordination means women's poor compliance with HSG procedures, so we use “poor compliance with HSG procedures” to replace “poor coordination” in line 82. Because of the pain, the patients can not cooperate well with HSG procedures. It will lead that HSG procedures be conducted unsuccessfullly. Thank you.

6. Background - Paragraph 3 - This includes one very long sentence ('Although studies have shown...') which is difficult to follow. I suggest this would benefit from review and reduction.
Response: Thank you for your suggestion. We have corrected this sentence as your suggestion. We have changed the statements into: Although studies have shown that those analgesics have certain effects on HSG pain relief, Ahmad [15] conducted a systematic review and meta-analysis of related randomized controlled trials and reported that there is no consensus concerning the optimal analgesic or timing of its pain administration. We have highlighted it in red. Thank you very much!

7. Background - Paragraph 3 - You note that patients receive no analgesics during HSG as routine care, is this a reflection of your own institution or more generally. It would be useful to be specific here to help to contextualise for the reader.
Response: Thank you for your suggestion. In paragraph 3, We have specifically note that patients receive no analgesics in our institution in line 93-94. Thank you.

8. Background - Paragraph 4 - You mention 'immersive VR'. It would be helpful to explain this concept in a little more detail, to help to contextualise for the reader.
Response: Thank you for your suggestion. The essence of immersive VR is the user’s illusion of going inside the 3D computer-generated world through a head-mounted device, as if the virtual world is a place the user is visiting. We have put this sentence into the new submission to explained the concept of immersive VR in line 98-100. It is highlighted in red. Thank you very much!

9. Methods - Study Design - Is your study design superiority or inferiority etc?
Response: Thank you for your suggestion. Our study design is no superiority or inferiority etc. Our design aims to test the difference between those two groups. When we begin to design it, we have no idea whether the VR can relieve the pain for women during HSG. We use a pilot trial to determine the sample size. Thank you.

10. Methods - Study Setting - This includes one very long sentence ('This institution...') which is difficult to follow. I suggest this would benefit from review and reduction.
Response: Thank you for your suggestion. We have corrected this sentence as your suggestion. We have changed the statements into: This institution is an urban, public, specializing in maternal and child care, tertiary-care teaching hospital in Ningxia Hui Autonomous Region located in Northwest China. Annually 50,000 patients are in treatment at the fertility clinic and approximately 1,000 hysterosalpingography are performed each year in this institution. We have highlighted it in red. Thank you very much!

11. Methods - Study Setting - What is your expected duration of recruitment?
Response: Thank you for your suggestion. We expect to complete recruitment within 10 months. We put this sentence into the study setting section. We have highlighted in red.

12. Methods - Study Participants - What does 'Indications for HSG' mean? Can this be detailed further?
Response: Thank you for your suggestion. According to the worldwide literature, indications for HSG included infertility, recurrent miscarriage, and miscellaneous. So we use “indications for HSG included infertility, recurrent miscarriage, and miscellaneous” to replace “indications for HSG” in line 130-131. Thank you.
13. Methods - Study Participants - What does 'Operator Difficulty' mean? Can this be detailed further? Response: Thank you for your question. When it is going smoothly, the whole procedure of HSG lasts about 20 minters. Because of some special situations like cervical adhesion or congenital variation, it is difficult to insert the 4mm sterile uterus radiography balloon catheter into the uterine cavity. In this situation, patients feel too painful to cooperate with the operator especially when injecting air into the aerocyst, which can stretch out the uterus. It will spend more time to finish the procedure. The patients will suffer incredible pain during the procedure. Severe pain will lead to false-negative results for tubal obstruction. We have underlined in red. Thank you.

14. Methods - Study Participants - What does 'All healthcare workers...will be willing to participate' mean? Presumably participation is for the patients not the professionals, who would be doing their routine clinical work with these patients? Response: Sorry for making such a ambiguity. In the radiology department, the HSG procedure will be carried out on each weekday by two gynecology assistants. The results of the HSG will be analyzed by a chief radiologist. We mean that: those healthcare workers who involved in this study were asked their willingness to participate. We will obtain healthcare workers’ consent before recruitment. Informed consent is generally used for objects of study rather than researchers. At this point, our presentation may confuse the reader. After receiving your valuable comments to this sentence, we have considered how to improve it for several times. We have tried to use “We will obtain the consents of the healthcare workers involved in this study” to replace “All healthcare workers involved in this study will be willing to participate”. We still think the modified sentence is easy to confuse the readers and makes no sense in the context. At last, we decide to withdraw this sentence. Thank you!

15. Methods - Study Participants - How will recruitment take place? Have any strategies been identified or implemented to help recruitment? Some further detail on this would be helpful.
Response: Thank you for your suggestion. As there are many problems in this sections, we have reworked to make sure to reflect clearly the process of recruitment. So we have built the Recruitment section in new submission. Here is the contain of the Recruitment section: The recruitment will take place in the radiology department of Yinchuan Women and Children Healthcare Hospital. Participants of the study will be recruited through Wechat advertising and posters in the infertility clinic. After the patients arrive at the radiology department, a screening of participants eligible for the study will be carried out, which includes a free preliminary physical examination, checking of the inclusion/exclusion criteria. The potential participants will receive information about the aims, benefits, and latent risks of the study from the protocol designer. If the patients wish to participate, they will be asked to sign an informed consent form that they agree to participate in the study and are willing to let the protocol designer publicize the research results including pictures. Participants are entitled to withdraw from the study at any time and this will not prejudice their subsequent treatment. The whole process of recruitment follows the principle of respect for autonomy. Thank you very much!

16. Methods - Randomisation - Is any form of stratification used?
Response: Thank you for your question. No stratification is used in our study design.

17. Methods - Randomisation - How is the randomisation sequence implemented - who completes this? are individual participant envelopes used? Be more specific to aid replication.
Response: Thank you for your question. The randomization sequence of each participant will be generated in advance with a computerized randomized number generator (random.org). It is performed by a statistical expert who is not involved in this trial. Individual participant envelopes will not be used.
A sealed opaque envelope will be used to store the randomization sequences. The random number table will be kept confidential by the full-time secretary of this project. We have expressed further as you suggest in randomization section. Thank you very much!

18.Methods - HSG procedures/VR Prototype/Interventions - It feels that this would benefit from some reworking, to streamline the description. I suggest it might be useful to start with a description of how participants will be recruited and consented, followed by details of the HSG procedure, followed by details of the intervention element, followed by details of the control.
Response: Thank you for your suggestion. We have reworked and streamlined the description and rearranged the order of those paragraphs and sentences as you suggest to make the whole method section easy to understand. Thank you very much!

19.Methods - Interventions - What does 'participants will be numbered according to the order of operation' mean? Further description is required.
Response: Sorry for making such a ambiguity. As there are many problems in Recruitment and Interventions sections, We have reworked to streamline the description. 'participants will be numbered according to the order of operation' means 'participants will be numbered according to the order of HSG'. We withdraw this sentence to avoid misunderstand. Thank you!

20.Methods - Measurement - What information will you collect at Baseline?
Response: Thank you for your question. Participants’ demographic data, relevant medical history, baseline anxiety level, as well as pulse rate, digital monitoring of oxygen saturation, and noninvasive monitoring of blood pressure, will be collected at baseline (T0) before the procedure. We have pointed out the information we will collect at Baseline in line 238-240. We have underlined in red.

21.Methods - Measurement - Given the study type and setting, I expect that retention will not be a significant issue here. It would be useful though to be clear about whether you have considered any specific mechanisms to ensure data collection is completed.
Response: Thank you for your question. To promote participant retention, every woman who completes all data collections will receive a free overall analysis of the HSG results by an experienced gynecologist. Because of the huge population base, there are a large number of patients in the infertility clinic in china. Every patient only gets a few minutes to talk with a doctor. Especially in our institution, patients in the infertility clinic are very difficult to obtain the overall analysis of the HSG results. The results of the pilot trial had shown that the specific design goes well. Data collection was completed well according to the plan. I have supplemented the sentence “To promote participant retention, every woman who completes all data collections will receive a free overall analysis of the HSG results by an experienced gynecologist.” into the Measurement section in this submission. We have highlighted it. Besides, to guarantee data quality, an independent clinical research assistant will verify the completeness and accuracy of data by review of medical records once a month. We have highlighted in red in the Data storage section. Thank you very much!

22.Methods - Measurements - It would be useful to provide some additional detail for the measurements e.g. what physiological parameters will be collected, and to detail when specific outcomes will be collected.
Response: Thank you for your suggestion. Physiological parameters including pulse rate (P), blood pressure (BP), and oxygen saturation (SpO2) will be collected. We have mentioned in line 208-209. (We have underlined in red). We also have set out the time every outcome will be collected in the last paragraph of the Measurements section. Thanks again.

23.Methods - Data Monitoring - Are there any other committees involved in this study? Is there any planned audit or monitoring? Are there any planned interim analyses?
Response: Thank you for your question. There are no other committees involved in this study. No funds have been used during the process of this trial. Thus no need to audit the funding. Regular DMC meetings will be held to monitor the progress of the study. We have mentioned in the Data monitoring section. Since our institution has sufficient patients, the recruitment won't take long before finish it. So, we do not plan interim analyses. Thank you very much!

24.Methods - Data Monitoring - Are the DMC members also independent of the study team recruiting and treating patients? Where protocol changes are required how will these be implemented?
Response: Thank you for your question. Some DMC members take part in our study as HSG operators or HSG results reviewer. The partial DMC members are not independent of the study team recruiting and treating patients. In regular DMC meetings, they discuss project issues, modify the study design and convey the protocol changes to the project implementer. The implementer will carry out according to the modified protocol. Thank you very much!

25.Methods - Data Storage - How will participant confidentiality be protected? Are there any data entry checks included e.g. double data entry? checking of entered data?
Response: Thank you for your question. Collected paper-based materials will be stored in locked filing cabinets in a locked office in Ningxia Medical University. Paper-based materials will not be stolen. All data will be collected password-protected digital files on a password-protected computer in a locked office. Digital data will not be stolen. Data entry will be performed continually throughout the study using the double-entry method. When the investigator inputs the information into the computer, each participant will be given a unique numeric code (ID Number). As a result, the data acquired from patients are individually identifiable by the research team members only. Only de-identified information will be presented or published. To improve data quality, an independent clinical research secretary will verify the completeness and accuracy of the data by review of medical records once a month. Authorship will follow guidelines recommended by the International Committee of Medical Journal Editors (ICMJE). We have made some modification in the Data storage section and highlighted in red. Thanks again.

26.Methods - Sample Size - You note use of previous studies to determine the sample size, but then also note a pilot. This section needs some clarity as to the sources of information used to determine your sample size.
Response: Thank you for your question. We use a pilot trial to determine the sample size. We have highlighted it in red. Thanks again.

27.Methods - Sample Size - Please confirm your calculation of drop out rate; 120% of 158 is not 200.
Response: Thank you for your question. When calculating the sample size, we had reference literature
published in trials entitled “Safety of early oral feeding after total laparoscopic radical gastrectomy for gastric cancer (SOFTLY): Study protocol for a randomized controlled trial”. The original sentences of this literature are “Considering both clinical and statistical considerations like intolerance of enteral nutritions, therefore, no less than 160 participants (80 participants in each group) will be required. Allowing for a 20% drop-out and withdrawals before trial completion, we decided to recruit a total of 200 participants (100 participants in each group).” We use a pilot trial to determine the sample size. These data collected from the pilot trial were plugged into the formula, and an n value of 157.02 was obtained. Thus, the rounded total sample size of the two groups was 158 (79 participants in each group). Allowing for a 20% dropout rate, a total of 190 participants were obtained. Because there are sufficient patients in our institution and we also consider some withdrawals before study completion, we decided to enroll a total of 200 participants (100 participants in each group) according to this literature published in trails. We guess this sample size determination is not following the specified standards, so we decided to correct our fault in the Sample size determination section. Thanks again.

28.Methods - Statistical analysis - Will the analyst be independent to the researchers recruiting and treating participants? Will the analyst be blinded to treatment allocation during analysis?
Response: Sorry for making such a ambiguity. The statistician, from the School of Public Health and Management of Ningxia Medical University, is independent of the researchers recruiting and treating participants and be blinded to treatment allocation during analysis. We have made some modifications in the Statistical analysis section. We have highlighted it in red. Thanks again.

29.Methods - Statistical analysis - Please provide more detail on the analytical methods to be used for the primary outcome analysis?
Response: Thank you for your question. The CONSORT guidelines for reporting of “parallel-group randomized controlled trials” recommend that both ITT and PP analyses should be reported for all planned outcomes to allow readers to interpret the effect of an intervention. When comes to compare the primary outcome between those two parallel groups, additional per-protocol analysis will be performed, and reasons for any protocol violations will be reported. We have added it to the Statistical analysis section. Thank you very much!

30.Methods - Statistical analysis - Will a separate analysis plan be generated?
Response: Thank you for your question. A complete statistical analysis plan will be generated in advance by the trial statistician. We are very sorry that we had not mentioned in the previous manuscript. We have corrected our fault in new submission. Thank you!

31.Discussion - Sentence 2 - 'Hence the ideal...' this doesn't seem to fit with subsequent sentences. I wondered if this might be better situated at the end of Paragraph 2/start of paragraph 3?
Response: Thank you for your suggestion. According to context, we think it is more appropriate to put this sentence at the end of Paragraph 1. The modified context is: “Although none of the study patients reported side effects, the risk of inhibition of respiration after opioids administration necessitates continuous monitoring. The ideal analgesic in outpatient operations would have the characteristics of both providing adequate pain control and the absence of significant adverse effects. For safety, opioids are effective in pain management during HSG, but cannot be used in outpatient settings.” Thank you!
32. Discussion - Limitations - You note a multi-centre study would be more representative. Is this planned at this time?
Response: Thank you for your question. We have no plan to do a multi-center study this time. Because our institution has sufficient patients. Annually 50,000 patients are in treatment at the fertility clinic and approximately 1,000 hysterosalpingography is performed in this institution. So this institution is a representative institution in Ningxia province on the HSG aspect. So we do not plan to do a multi-center study this time. In the future, we will perform the multi-center study. Thank you!

33. Availability of Data - Will the data derived from this work be accessible?
Response: Sorry for not having a clearly stated. After this study is completed, the final dataset and statistical codes will be accessible from the corresponding authors with reasonable requests, except for patients' personal information. We have made some modifications in the Availability of Data section. We have highlighted in red. Thank you very much!

34. Figure 1 - It would be useful to note in this diagram the point at which eligibility is assessed, consent taken and Baseline data collected.
Response: Thank you for your suggestion. We have made some modifications in Figure 1 according to your suggestion. We have highlighted in red. Thank you very much!

35. Spirit Checklist - Where elements are not applicable and so noted as ' --', it would be helpful for transparency to document why this is not relevant here.
Response: Thank you for your suggestion. We have made some modifications according to your suggestion. Thank you very much!

Reviewer #2
This submissions provides the protocol of a well planned trial taking key elements of trial processes into consideration. A clear rational for the trial and interest in the intervention is offered. I offer some minor points of feedback and ask for more explicit information within your protocol:

1. I am aware that recruitment to the trial has commenced, however, I suggest that you ensure that the section on recruitment (see page 9 under the heading titled "Interventions") reflects clearly the process employed and the underpinning ethical principles. "The patients who meet all pre-specified eligibility and exclusion criteria will be drafted into this study ...." does not convey a message of choice or informed consent prior to enrolment.
Response: Thank you for your suggestion. As there are many problems in this section, we have reworked to make sure to reflect clearly the process of recruitment and the underpinning ethical principles. So we have built the Recruitment section in the new submission. Here is the content of the Recruitment section: The recruitment will take place in the radiology department of Yinchuan Women and Children Healthcare Hospital. Participants of the study will be recruited through Wechat advertising and posters in the infertility clinic. After the patients arrive at the radiology department, a screening of participants eligible for the study will be carried out, which includes a free preliminary physical examination, checking of the inclusion/exclusion criteria. The potential participants will receive information about the aims, benefits, and latent risks of the study from the protocol designer. If
the patients wish to participate, they will be asked to sign an informed consent form that they agree to participate in the study and are willing to let the protocol designer publicize the research results including pictures. Participants are entitled to withdraw from the study at any time and this will not prejudice their subsequent treatment. The whole process of recruitment will follow the principle of respect for autonomy. Thank you very much!

2. Please review your section on data storage - where is the location of the "locked filing cabinet"; what data protection guidelines inform the proposed actions?
Response: Thank you for your suggestion. We have corrected our fault in the Data storage section. Collected paper-based materials will be stored in locked filing cabinets in a locked office in Ningxia Medical University. The security operation for Ningxia Medical University is powerful. Authorship will follow guidelines recommended by the International Committee of Medical Journal Editors (ICMJE). We have highlighted it in red. Thank you very much!