PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Use of immersive virtual reality for stress reduction during botulinum toxin injection for spasticity (RVTOX), a study protocol of a randomized control trial
AUTHORS	Bougeard, Marie; Hauret, Isabelle; Pelletier-Visa, Mathilde; PLAN-PAQUET, Anne; Givron, Pascale; Badin, Marin; Pereira, Bruno; Lanhers, Charlotte; Coudeyre, Emmanuel

VERSION 1 – REVIEW

REVIEWER	Bicego, Aminata University of Liege, Sensation and Perception Research Group - GIGA Conscisouness
REVIEW RETURNED	22-Sep-2022

GENERAL COMMENTS	This study protocol aims to assess the effect of immersive virtual reality (VR) on stress and pain in adults undergoing botulinum toxin injection for spasticity. As VR gains more and more interest in the medical field, it is important to publish protocols on the topic. Nevertheless, in its current state, the manuscript requires significant revisions before it can be considered for publication. A native speaker and a statistical expert should revise the manuscript before re-submission. Title: The title does not mention that it is a research protocol. This should be mentioned in the title. Key-words: The key-words selected by the authors do not represent the research. They should be changed to better represent the study. It is indeed odd that the study assesses the effect of immersive VR on stress and pain and that none of these words figure in the key-words. Abstract: In general, authors should use the same tenses throughout the manuscript. They should use the future as the study has not been carried out yet. Acronyms should not be used in the abstract. L14: “Immersive virtual reality is a digital technique that stimulates the environment around a person.” Do the authors mean “simulates”? If not, could they explain what they mean by “stimulates”. L30-31: “CHU” is a French term, authors should use the English. L35: authors should explain the “control”. Is it a control group? If so, they should explain what is the control group. L41: Could the authors explain how such design allows to consider the injection as “a statistical individual” and explain what they mean by “a statistical individual”? Strengths and limitations of this study: L29: Authors should be consistent when they write about the same things throughout the manuscript.

	Is it a randomized quasi-experimental study or a stepped wedged randomized controlled clinical trial? L3: The aim is not the same as in the abstract. Is the aim to reduce stress and pain? Is the aim to augment tolerance? Authors should be consistent. L40: this sentence should be rephrased; it is not understandable. No limitations are mentioned. Introduction: General comment: The introduction needs to be supported by more references. The focus of the paper is on immersive VR. The authors should further explain what immersive VR is compared to interactive and contemplative VR. They mention presence and immersion but don't explain what these concepts are. In the abstract, the authors write that the pain causes the anxiety which implies that there is a causal relationship of pain against stress. They should justify their statement with a reference. Moreover, the link they mention is not clear here. It seems that patients experience pain and stress in a none causal way. Page5 L16: According to the citation they cite, the main first cause of pain is the stimulation and in second position the needle insertion. The authors should adequately cite the results of studies they cite. L45: […] technique that stimulates […]. Do the authors mean "simulates"? L50: The authors cite a paper on presence as a reference. In order to have a high sense of presence in the VR, the environment does not need to resemble real world. It can be a fake world that induces a high immersion and thus a high sense of presence. Authors should cite adequate reference according to the statements they make. L51: Could authors explain how one can interact with the sight and the hearing? L56: Is immersion the only factor? Isn't presence an important factor as well? Are there other factors ? Page6 L11: "the reduction of pain in treating burn injuries (13–17)," the citations are not all about burn injuries. The authors should be careful to cite references accurately. L18: since only few studies exist on the topic it might be interesting to detail a little bit more the ones that exist. L37: the aims are the same as in the abstract but different from the strengths and limitations sections. Authors should be consistent. Methods and Analyses Trial design: Overall the design and procedure lack clarity and coherence. Authors should revise the entire section. L8: As of now, the authors have used three different terms to mention their design. They should use the same term throughout the manuscript. L9: Could the authors explain the blinding procedure? When using a VR device, it is impossible to blind the therapist and the patients. L14: "The design and conduct […]". Could the authors explain what they mean by conduct? To they mean "procedure"? L27: "This design considers the injection as a statistical individual." Please explain how. L29: Table one does not represent "a flow of participants" but rather

	it represents the design of the study. Table1: throughout the manuscript the authors mention two groups while three groups figure in table 1. The authors should be clearer. L57: “CHU” is French. Authors should use English. Page8: Exclusion criteria: - it is odd that no impaired vision or hearing figure in the exclusion criteria as they are mandatory for the patients to benefit the VR device. - dermatological problems should be an exclusion criterion - Major cognitive disorder: could authors be more specific? What do they mean? Will it be assessed by a standardized tool? If so, which one? - Any medical condition deemed by the investigator to be incompatible with the research. Could the authors be more specific? Give some examples perhaps. - MEOPA: this should be in English. Acronyms should be put in parenthesis not the other way around. - Medical treatment or condition that may disturb heart rate variability. Could the authors specify their statement? - Refusal to participate: is this an exclusion criterion? Interventions: Overall, authors should explain the intervention in detail. They mention that the patients will have the choice between five different scenarios. They should be explained. Maybe adding some images of each scenario might be useful for other clinicians. Will the device be disinfected between each patient? This should be mentioned. Page9 L9: […] and ice analgesia for palmar or plantar injections […]. How do the authors plan to distinguish the analgesic effect of ice and the one of VR? The primary and secondary outcomes are not clearly explained. “Another secondary outcome is the quality of conditions under which the injections were given, as assessed by the physician immediately after the end of the injection on a numerical scale ranging from 0 “extremely poor conditions” to 10 “extremely good conditions”.” What do the authors mean by “the quality of conditions”? since it is the first time that this outcome is mentioned authors could be more explicit about it. Statistical considerations It is odd that this is a section in its own right when the analyses are part of the title of the previous section. Generally, this section needs to be significantly revised. No clear statistical test is mentioned. The sample calculation also lack clarity. It is also unclear how (with what statistical test) the authors will answer their research questions. This should be revised by an expert in statistics. Discussion The discussion is quite poor. Authors should discuss their hypotheses according to the existing literature and the eventual limitations.

	References: The references are not all in the same format. They also include French, everything should be in English.

REVIEWER	Găină, Marcel Grigore T Popa University of Medicine and Pharmacy Faculty of Medicine, 3rd Medical, Psychiatry
REVIEW RETURNED	25-Nov-2022

GENERAL COMMENTS	Regarding the proposed protocol entitled: „Use of immersive virtual reality for stress reduction during botulinum toxin injection for spasticity” The conceptualisation of this protocol seems flawless, and embedds the state-of-the-art overview of current progress regarding virtual reality randomised control trials. Still, there are a few suggestions I would like to underline: 3rd page , Line 7 to 8: I kindly suggest making the sentence less complex by rephrasing „Botulinum toxin injection is a commonly used treatment to help reduce body spasticity associated with central neurological damage such as cerebral stroke, multiple sclerosis or traumatic brain injury similarly” to something similar to: Botulinum toxin injections are a common way to help reduce spasticity in the body caused by.... Line 14 to line 15 – ”Immersive virtual reality is a digital technique that stimulates the environment around a person” Immersive virtual reality SIMULATES or EMULATES an a digital environment in order to resemble a real environment ; perhaps a rephrase is needed to reveal a clearer perspective. Line 20 to 24 . ”The purpose of this study was to evaluate whether using immersive virtual reality can reduce the level of stress and level of pain adults experience during botulinum toxin injection” could become clearer by rephrasing to ”Virtual reality can help adults cope with the stress and pain of botulinum toxin treatment injection.” Line 33 to 35 : ”hypothesis will be tested with a stepped wedge randomized method comparing a non-invasive technique” to ”The research hypotheses will be tested using a randomized stepped wedge method versus a non-invasive technique.” Line 41 to 43 Such a design leads to consider the injection as a statistical individual. To Such a design leads to considering the injection as a statistical individual (is the meaning statistical individual variable?). Page 4 line 18 Strengths and limitation of this study should be changed to strenghts and limitationS of this study: Line 40 : Although stress is an abstract notion, it will be studied by heart rate variability. To : Although stress is an abstract notion, it will be studied through heart rate variability. Page 5 line 40 Immersive virtual reality is a digital technique that stimulates the 3D spatial and sound environment around a person said to be immersed in this virtualized world to SIMULATES not stimulates. Page 7 line 10 - This is a controlled, randomized, clustered therapeutic trial with sequential permutation. It is a single-blind, single-center therapeutic trial comparing a non-invasive technique (helmet with virtual reality) to its control (helmet with no image or audio). Virtual reality Headset

	Page 8 – line 20 to 23 local contraindication of wearing a mask (lesion of the face or the skull) Authors should note that you will not be able to use a mask along with a virtual reality headset because the warmth of exhaled air will blur the lens, impairing vivid immersion of the user. Line 39-40 Exclusion criterias should also explicitly state cardiovascular diagnosis of rhythm perturbances or priorly diagnosed anxiety disorders, that may hinder results. Instead of ”Medical treatment or condition that may disturb heart rate variability” Page 8 line 57 Virtual reality and control (virtual reality without sound and image) – how are you going to manage to clinically realise this aspect? I suggest you check into the EaseVR study protocol, a currently FDA Approved device, that managed to effectively realise the blinding process - Garcia, L.M.; Birckhead, B.J.; Krishnamurthy, P.; Sackman, J.; Mackey, I.G.; Louis, R.G.; Salmasi, V.; Maddox, T.; Darnall, B.D. An 8-Week Self-Administered At-Home Behavioral Skills-Based Virtual Reality Program for Chronic Low Back Pain: DoubleBlind, Randomized, Placebo-Controlled Trial Conducted During COVID-19. J. Med. Internet Res. 2021, 23, e26292 Page 13, line 6 ”Participants requiring botulinum toxin injection therapy will be recruited during rehabilitation consultations” could be rephrased to ”During rehabilitation, six participants who require botulinum toxin injection therapy will be recruited.” Finally, I would like to congratulate the group of authors for undertaking such a demanding task, and pledge to offer my support by any means necessary for contributing to the development and implementation of immersive virtual reality in medical sciences.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Aminata Bicego, University of Liege

Title: The title does not mention that it is a research protocol. This should be mentioned in the title. Use of immersive virtual reality for stress reduction during botulinum toxin injection for spasticity (RVTOX), a study protocol of a randomized control trial

Key-words: The key-words selected by the authors do not represent the research. They should be changed to better represent the study. It is indeed odd that the study assesses the effect of immersive VR on stress and pain and that none of these words figure in the key-words.
Key words were adapted to mesh terms.

Abstract:

In general, authors should use the same tenses throughout the manuscript. They should use the future as the study has not been carried out yet. Acronyms should not be used in the abstract.

L14: “Immersive virtual reality is a digital technique that stimulates the environment around a person.” Do the authors mean “simulates”? If not, could they explain what they mean by “stimulates”.
Done, thank you

L30-31: “CHU” is a French term, authors should use the English.
Changed to : Clermont-Ferrand University Hospital in the department of Physical Medicine and Rehabilitation.

L35: authors should explain the “control”. Is it a control group? If so, they should explain what is the control group.
The control group receive headset with no image nor audio.

L41: Could the authors explain how such design allows to consider the injection as “a statistical individual” and explain what they mean by “a statistical individual”?
We thank the reviewer for the helpful comment. As each patient will receive four injections after a first injection in usual condition (in order to measure baseline values, especially for the primary endpoint, HRV), the statistical unit will be the injection. So, the statistical analysis will be performed by using random-effects model taking into account between and within patient variability (patient as random-effect). “Statistical individual” has been replaced by “statistical unit” which seems clearer, according to the reviewer’s comment.[PB1]

Strengths and limitations of this study:

L29: Authors should be consistent when they write about the same things throughout the manuscript.

Is it a randomized quasi-experimental study or a stepped wedged randomized controlled clinical trial?
We thank the reviewer for the comment. As discussed by Miller et al. (Psychiatry Research, 2020), stepped wedged randomized controlled clinical trial can be considered as quasi-experimental study: *“Many implementation science questions can be feasibly answered by fully experimental designs, typically in the form of randomized controlled trials (RCTs). Implementation focused RCTs, however, usually differ from traditional efficacy- or effectiveness-oriented RCTs on key parameters. Other implementation science questions are more suited to quasi-experimental designs, which are intended to estimate the effect of an intervention in the absence of randomization. These designs include pre-post designs with a non-equivalent control group, interrupted time series (ITS), and stepped wedges, the last of which require all participants to receive the intervention, but in a staggered fashion”.*
Furthermore, second reviewer did no comment this suggestion.
We propose not to modify the manuscript.

L3: The aim is not the same as in the abstract. Is the aim to reduce stress and pain? Is the aim to augment tolerance? Authors should be consistent.
Sentence has been deleted.

L40: this sentence should be rephrased; it is not understandable.
Done

No limitations are mentioned.

Limitation were added :
The effect might be modest for patient who receive injections from many years, due to a habituation effect.

The tolerance of virtual reality might be different from a patient to another, and might be responsible for lost to follow up, but the number of patient needed to be include was calculated with this possibility.

Introduction:

General comment: The introduction needs to be supported by more references. The focus of the paper is on immersive VR. The authors should further explain what immersive VR is compared to interactive and contemplative VR. They mention presence and immersion but don't explain what these concepts are.
The following papers are added in the manuscript.
Buche H, Michel A, Piccoli C. Contemplating or Acting? Which Immersive Modes Should Be Favored in Virtual Reality During Physiotherapy for Breast Cancer Rehabilitation. Front Psychol. 8 apr 2021;12:631186.
Witmer, B. G., and Singer, M. J. (1998). Mesuring presence in virtual environnements: a presence questionnaire. Presence 7, 225–240.

In the abstract, the authors write that the pain causes the anxiety which implies that there is a causal relationship of pain against stress. They should justify their statement with a reference. Moreover, the link they mention is not clear here. It seems that patients experience pain and stress in a none causal way.
We agree, what we want to say is that participants of the study know how botulinum injections go, there is anxiety for the next injection.

Page5
L16: According to the citation they cite, the main first cause of pain is the stimulation and in second position the needle insertion. The authors should adequately cite the results of studies they cite.
Done

L45: […] technique that stimulates […]. Do the authors mean "simulates"?
Done. We meant "simulates".

L50: The authors cite a paper on presence as a reference. In order to have a high sense of presence in the VR, the environment does not need to resemble real world. It can be a fake world that induces a high immersion and thus a high sense of presence. Authors should cite adequate reference according to the statements they make.
Sentence changed to *"By visually isolating the patient from the medical context, it allows the individual's attention to focus on the virtual experience and be distracted from the unpleasant stimuli of the stressful environment".*

L51: Could authors explain how one can interact with the sight and the hearing?
I agree, Sentence deleted.

L56: Is immersion the only factor? Isn't presence an important factor as well? Are there other factors?
The following sentence has been added: *"One study showed an increase in positive emotions (i.e., joy and happiness) and a decrease in anxiety regardless which immersive support methods were offered: participatory virtual reality or contemplative".*

Page6
L11: "the reduction of pain in treating burn injuries (13–17)," the citations are not all about burn injuries. The authors should be careful to cite references accurately.
Thank you, I revised all my references.

L18: since only few studies exist on the topic it might be interesting to detail a little bit more the ones that exist.
Done

L37: the aims are the same as in the abstract but different from the strengths and limitations sections. Authors should be consistent.
Done

Methods and Analyses
Trial design:
Overall the design and procedure lack clarity and coherence. Authors should revise the entire section. This section was revised by a statistician.

L8: As of now, the authors have used three different terms to mention their design. They should use the same term throughout the manuscript.
See below

L9: Could the authors explain the blinding procedure? When using a VR device, it is impossible to blind the therapist and the patients.
The blinding procedure is for the investigator, not the doctor who is doing the injection. It was added in the manuscript.

L14: "The design and conduct […]". Could the authors explain what they mean by conduct? To they mean "procedure"?
We agree. It is procedure.

L27: "This design considers the injection as a statistical individual." Please explain how.
We thank the reviewer for the comment. As aforementioned, as each patient will receive five injections, the statistical unit will be the injection. The statistical analysis will be performed by using random-effects model taking into account between and within patient variability (patient as random-effect). Such design allows: (i) to measure the efficacy after several injections, (ii) to study the between and within patient variability and (iii) to increase the statistical power.

L29: Table one does not represent "a flow of participants" but rather it represents the design of the study.
It was changed thank you.

Table1: throughout the manuscript the authors mention two groups while three groups figure in table 1. The authors should be clearer.
We thank the reviewer for the relevant comment. We agree that submitted manuscript is not sufficiently clear concerning the definition of groups. Patients will be randomized into three steps (according to stepped wedge design), after a first injection in usual condition (in order to measure baseline values, especially for the primary endpoint, HRV) (1) those with a first injection in control condition and then three injections in virtual reality condition, (2) those with two first injections in control condition and then two injections in virtual reality condition and (3) those with three first injections in control condition and then one injection in virtual reality condition. The manuscript has been revised accordingly.

	First injection	**Second injection**	**Third injection**	**Fourth injection**	**Fifth injection**
Step 1	Standard conditions	Control	Control	Control	Virtual reality

Step 2	Standard conditions	Control	Control	Virtual reality	Virtual reality
Step 3	Standard conditions	Control	Virtual reality	Virtual reality	Virtual reality

L57: “CHU” is French. Authors should use English.
Done

Page8:
Exclusion criteria:
It is odd that no impaired vision or hearing figure in the exclusion criteria as they are mandatory for the patients to benefit the VR device.
Dermatological problems should be an exclusion criterion
It was changed thank you.

Major cognitive disorder: could authors be more specific? What do they mean? Will it be assessed by a standardized tool? If so, which one?
Done, we added the definition of the MMS scale

Any medical condition deemed by the investigator to be incompatible with the research. Could the authors be more specific? Give some examples perhaps.
Any medical condition deemed by the investigator to be incompatible with the research (eg : major cognitive disorders MMS < 24/30, impaired vision or hearing)

MEOPA: this should be in English. Acronyms should be put in parenthesis not the other way around. Changed to ENTONOX, the engliush version.

Medical treatment or condition that may disturb heart rate variability. Could the authors specify their statement?
Changed to *“Cardiovascular diagnosis of rhythm perturbances or priorly diagnosed anxiety disorders that may inder results“.*

Refusal to participate: is this an exclusion criterion?
We agree. We deleted.

Interventions:
Overall, authors should explain the intervention in detail. They mention that the patients will have the choice between five different scenarios. They should be explained. Maybe adding some images of each scenario might be useful for other clinicians.
Virtual reality scenario is chosen by the patient between 8 different scenarios (dunes landscape, mountain during summer or winter, Spitzberg landscape on a boat, mountain picnic in the Alpes, countryside in India, river and air ballon).
We added a scan of the choices in attached files.

Will the device be disinfected between each patient? This should be mentioned.
I added a part on disinfection, thank you.

Page9
L9: […] and ice analgesia for palmar or plantar injections […]. How do the authors plan to distinguish the analgesic effect of ice and the one of VR?
All participants are their own control and will be compared with themselves through every injections.

The primary and secondary outcomes are not clearly explained.

“Another secondary outcome is the quality of conditions under which the injections were given, as assessed by the physician immediately after the end of the injection on a numerical scale ranging from 0 “extremely poor conditions” to 10 “extremely good conditions”.” What do the authors mean by “the quality of conditions”? Since it is the first time that this outcome is mentioned authors could be more explicit about it.
We deleted this secondary outcome.

Statistical considerations
It is odd that this is a section in its own right when the analyses are part of the title of the previous section.
It is asked in the BMJOpen rules for a research protocol.

Generally, this section needs to be significantly revised. No clear statistical test is mentioned. The sample calculation also lack clarity. It is also unclear how (with what statistical test) the authors will answer their research questions. This should be revised by an expert in statistics.
We thank the reviewer for the comment. We agree that statistics section must be revised.

Sample size estimation
In order to evaluate the effect of virtual reality on stress during botulinum toxin injections, the heart rate variability will be compared between groups (control vs. virtual reality). Using the log LF/HF as primary endpoint, 24 patients will be required to highlight a clinically relevant difference of 0.2 for a standard-deviation equals 0.3, a two-sided type I error of 5%, and a statistical power greater than 80%, according to the results reported by Dutheil and al (19,20). Due to design with sequential permutations, 42 patients will be included to take into account between and within patient variability measured by intra-class correlation coefficient fixed at 0.25. The rate of lost to follow up should benegligible, as this is a conventional care pathway.

Statistical analysis
All analysis will be performed with the Stata software (version 15, StataCorp, College Station, US).
Continuous variables will be presented as mean and standard-deviation or median and interquartile range. The assumption of normality will be assessed by using the Shapiro-Wilk test. Patients will be described and compared between three steps for the following inclusion variables: eligibility criteria, epidemiological and clinical characteristics. A difference will be determined on the basis of clinical and statistical considerations. The type I error will be 5% two-sided. A description of the protocol deviations and the causes of lost to follow-up will be carried out.
The primary analysis will be conducted in intention-to-treat sample. A per-protocol analysis will be then conducted.

Primary analysis
The main objective of this study is to assess the effect of virtual reality on stress during botulinum toxin injections. Due to randomized stepped wedge design, the primary analysis will be based on a comparison of the primary endpoint (heart rate variability) between groups (control vs. virtual reality) by random-effects model taking into account between and within patient and step variabilities (patient and step considered as random-effects). The results will be expressed with effect-size and 95% confidence interval.

Secondary analyses
In order to assess the effect of repeated use of virtual reality, particular attention will be given to the analysis of group (control vs. virtual reality) x injection (second to fifth) interaction evaluated as a fixed effect in the aforementioned mixed models.
The primary analysis will be completed by multivariate analysis (i.e. multiple linear regression) to take into account possible confounding factors chosen according to the univariate results and to their clinical relevance (such as age, gender, social economic status, disease duration). The normality of

residuals will be studied as aforementioned. If necessary, the dependent variable will be transformed (logarithmic transformation). The results will be expressed with effect sizes and 95% confidence intervals.
Subgroup analyses will be conducted for the primary endpoint to evaluate effect of virtual reality according to age, gender, social economic status and disease duration. The subgroup x group (control vs. virtual reality) interaction will be assessed.
Continuous secondary endpoints (pain, heart rate) will be compared between control and virtual reality groups with analogous statistical analysis plan those described for primary endpoint. For categorical endpoints, the comparisons between control and virtual reality groups will be performed with mixed generalized linear regression model. The results will be expressed in terms of absolute differences, odds-ratios and 95% confidence intervals.
The following parameters were collected: root mean square of successive differences between normal (RMSSD), standard deviation of the normal sinus beats (SDNN), percentage of adjacent NN intervals that differ from each other by more than 50 milliseconds (pNN50), total power, and frequency-domain measurements to separate HRV into its component VLF (very low frequency), LF (low frequency), LF/HF and HF (high frequency) rhythms that operate within different frequency ranges.(22) The relationship between these parameters will be analyzed using correlation coefficient (Pearson or Spearman, according to statistical distribution) and applying Sidak's type I error correction for multiple comparisons.
A sensitivity analysis will be conducted to determine the statistical nature of missing data and then to propose the most appropriate method of data imputation (maximum bias or multiple imputation).

Discussion
The discussion is quite poor. Authors should discuss their hypotheses according to the existing literature and the eventual limitations.
Limitations were added to the discussion. Yet, if I may, it is a study protocol, so the discussion tends to be poor either way, as the study has not yet started.

References:
The references are not all in the same format. They also include French, everything should be in English. I changed everything in english thank you.

Reviewer: 2
Dr. Marcel Găină, Grigore T Popa University of Medicine and Pharmacy Faculty of

3rd page , Line 7 to 8: I kindly suggest making the sentence less complex by rephrasing „Botulinum toxin injection is a commonly used treatment to help reduce body spasticity associated with central neurological damage such as cerebral stroke, multiple sclerosis or traumatic brain injury similarly" to something similar to: Botulinum toxin injections are a common way to help reduce spasticity in the body caused by....
Thank you for your help rephrasing.

Line 14 to line 15 – "Immersive virtual reality is a digital technique that stimulates the environment around a person" Immersive virtual reality SIMULATES or EMULATES an a digital environment in order to resemble a real environment ; perhaps a rephrase is needed to reveal a clearer perspective.
Yes indeed, I meant SIMULATES

Line 20 to 24. "The purpose of this study was to evaluate whether using immersive virtual reality can reduce the level of stress and level of pain adults experience during botulinum toxin injection" could

become clearer by rephrasing to ”Virtual reality can help adults cope with the stress and pain of botulinum toxin treatment injection.”
Thank you for you help rephrasing.

Line 33 to 35 : ”hypothesis will be tested with a stepped wedge randomized method comparing a non-invasive technique” to ”The research hypotheses will be tested using a randomized stepped wedge method versus a non-invasive technique.” [PB2]
We thank the reviewer for the proposal. The manuscript was revised accordingly.

Line 41 to 43 Such a design leads to consider the injection as a statistical individual. To Such a design leads to considering the injection as a statistical individual (is the meaning statistical individual variable?).[PB3]
We thank the reviewer for the proposal. The manuscript was revised accordingly.

Page 4 line 18 Strengths and limitation of this study should be changed to strengths and limitations of this study:
Done, thank you

Line 40 : Although stress is an abstract notion, it will be studied by heart rate variability. To: Although stress is an abstract notion, it will be studied through heart rate variability.
Done, thank you

Page 5 line 40
Immersive virtual reality is a digital technique that stimulates the 3D spatial and sound environment around a person said to be immersed in this virtualized world to SIMULATES not stimulates.
Thank you, I changed to SIMULATES.

Page 7 line 10 - This is a controlled, randomized, clustered therapeutic trial with sequential permutation. It is a single-blind, single-center therapeutic trial comparing a non-invasive technique (helmet with virtual reality) to its control (helmet with no image or audio). Virtual reality Headset
Thank you for your help, yes indeed it is clearer.

Page 8 – line 20 to 23 local contraindication of wearing a mask (lesion of the face or the skull)
Done

Authors should note that you will not be able to use a mask along with a virtual reality headset because the warmth of exhaled air will blur the lens, impairing vivid immersion of the user.
We wanted to say headset and not mask. Thank you for the comment.

Line 39-40 Exclusion criterias should also explicitly state cardiovascular diagnosis of rhythm perturbances or priorly diagnosed anxiety disorders, that may hinder results. Instead of ”Medical treatment or condition that may disturb heart rate variability”
Done
“*Cardiovascular diagnosis of rhythm perturbances or priorly diagnosed anxiety disorders that may inder results*”

Page 8 line 57
Virtual reality and control (virtual reality without sound and image) – how are you going to manage to clinically realise this aspect? I suggest you check into the EaseVR study protocol, a currently FDA Approved device, that managed to effectively realise the blinding process - Garcia, L.M.; Birckhead, B.J.; Krishnamurthy, P.; Sackman, J.; Mackey, I.G.; Louis, R.G.; Salmasi, V.; Maddox, T.; Darnall, B.D. An 8-Week Self-Administered At-Home Behavioral Skills-Based Virtual Reality Program for Chronic Low Back Pain: DoubleBlind, Randomized, Placebo-Controlled Trial Conducted During COVID-19. J. Med. Internet Res. 2021, 23, e26292

Thank you for this manuscript.
Our control will be similar to the one in your citation. Patients will be compared to themselves as well, by having the virtual reality device on, off and no device in the beginning.
The investigator is the only one in blinding process and not in the room during the therapy.

Page 13, line 6 ”Participants requiring botulinum toxin injection therapy will be recruited during rehabilitation consultations” could be rephrased to ”During rehabilitation, six participants who require botulinum toxin injection therapy will be recruited.”
Thank you, it was rephrased.

Finally, I would like to congratulate the group of authors for undertaking such a demanding task, and pledge to offer my support by any means necessary for contributing to the development and implementation of immersive virtual reality in medical sciences.

Reviewer: 1
Competing interests of Reviewer: None.

Reviewer: 2
Competing interests of Reviewer: I declare that I have no conflict on interest to declare regarding the review of this proposed randomised control trial protocol manuscript.