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Keywords:	REHABILITATION MEDICINE, NEUROLOGY, Pain management < ANAESTHETICS

Use of immersive virtual reality for stress reduction during botulinum toxin injection for spasticity

(RVTOX)

A research protocol for a randomized trial

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ABSTRACT

Introduction

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. Most patients experience significant stress because of the pain felt during the injection, the level of which varies among patients. Immersive virtual reality is a digital technique that stimulates the environment around a person. Only one study in pediatrics has shown that immersive reality technique has a positive impact on the level of pain and agitation experienced during botulinum toxin injection. No study has investigated the technique in adults. 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.

Methods and analysis

We will recruit adults from a cohort of patients receiving botulinum toxin injections on a regular basis in the Department of Physical Medicine and Rehabilitation at CHU Clermont-Ferrand. The research hypothesis will be tested with a stepped wedge randomized method comparing a non-invasive technique (helmet with virtual reality) to a control during botulinum toxin injection. Participants will undergo a first botulinum toxin injection without any device. Then, all participants will receive the control technique, then the control technique or the virtual reality, depending on the randomization plan. Finally, all participants will receive the virtual reality technique. Such a design leads to consider the injection as a statistical individual.

Ethics and dissemination

Participants will be fully and fairly informed in terms of their understanding of the objectives and constraints of the study and the possible risks involved. They will also be entitled to refuse the study and/or withdraw, and this refusal will have no impact on their follow-up. The investigator must inform the subjects of the opinion given by the CPP

Ethical approval was given by the CPP in January 2022.

ClinicalTrials.gov: NCT05364203

Date and version of the protocol: Version 2 of the protocol 08/03/2022

Keywords: Virtual reality, stress, pain, spasticity, botulinum toxin

Strengths and limitation of this study

- This study will be the first to assess the effects of immersive virtual reality on stress during botulinum toxin injection for spasticity in adults.
- In addition to being non-invasive and non-pharmacologic, virtual reality has multiple other advantages, including minimal adverse effects, low cost, easy accessibility and portability.
- The design of this study (randomized quasi-experimental study with sequential permutations) can meet the highest level of evidence.
- The expected benefit for patients is reduced stress and pain with the use of virtual reality during botulinum toxin injection. Therefore, the aim is to improve the tolerance of botulinum toxin injection for patients by using a virtual reality technique.
- Although stress is an abstract notion, it will be studied by heart rate variability.

INTRODUCTION

The effectiveness of botulinum toxin injection for spasticity has been widely demonstrated in people with brain lesions (1). Therefore, this treatment is used in many patients with central neurological deficit (stroke, multiple sclerosis, spinal cord injury, traumatic brain injury). Unfortunately, because the effect of intramuscular botulinum toxin injection is temporary (approximately 3 months), these injections must be repeated every 3 to 4 months. The tolerance of the injections varies among patients. The pain felt during the injection is mainly due to the needle insertion in the skin(2) and depends on the technique used (electrical stimulation) and the body site of the injection (palm and plantar injections are the most painful). Unfortunately, most patients experience significant stress during the injection.

Intramuscular injection of botulinum toxin decreases hypertonia (1). In fact, botulinum toxin injection has been a reference treatment for focal spasticity since the recommendations of the French *Agence nationale de sécurité du médicament et des produits de santé* of 2011. One study specifically studied the effect of virtual reality on pain during botulinum toxin injection in pediatrics.(3)

Various reactions of the body caused by stress are known to be related to a change in the autonomic nervous system, and stress can be assessed objectively by using biomarkers and heart rate variability (HRV)(4). Heart rate can be measured easily, non-invasively, reproducibly and painlessly (5). It reflects the cardiovascular response to regulatory impulses affecting heart rhythm (6). In general, HRV is a reliable indicator of autonomic nervous system activity(7), and many studies have used HRV for estimating mental stress (8–11).

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. This virtualized world is meant to closely resemble a real-world environment (12). For medical applications, a person could be made to feel as if they were in a totally different environment than a hospital. The person can interact with this environment and thus “live” a cognitive experience owing to the two main senses of sight and hearing. Immersion in this 360° audio-visual content allows the person to be less attentive during therapy. This technique has been used during painful procedures such as wound treatment(13), episiotomy suture(14), and other procedures (15). Solid evidence from controlled research suggests that

virtual reality distraction is effective for reducing experimental pain as well as the pain associated with burn injury care(16).

In recent years, several studies have focused on the effectiveness of virtual reality to reduce pain during various painful medical procedures,(15) the reduction of pain in treating burn injuries (13–17), and pain reduction during episiotomy repair (14). The effect of patients' clinical characteristics on pain during botulinum toxin injection has been studied (2). Use of virtual reality in hospitalized patients significantly reduced pain versus a control distraction condition. These results indicate that virtual reality is an effective and safe adjunctive therapy for pain management in the acute inpatient setting(18).

Few studies have investigated the pain felt during botulinum toxin injection. The only published studies concern the effect of the tracking technique. No studies have evaluated the effect of techniques to reduce stress and pain during injection in adults. The only publication concerns the pediatric population and showed decreased pain and agitation with use of virtual reality during botulinum toxin injection(3).

Therefore, the hypothesis of this research is that an immersive virtual reality system can reduce the stress and painful experience of botulinum toxin injection in adults. The study aims to evaluate the effect of virtual reality on stress induced by botulinum toxin injection.

METHODS AND ANALYSIS

Trial design

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).

The design and conduct of this trial will adhere to the requirements of the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT appendix). The results will be reported in accordance with the CONSORT Statement for non-pharmacologic trials.

The first injection session will involve standard conditions (without any virtual reality), then the next session will involve the helmet with no image or audio (control group). Then, participants will receive the control technique or virtual reality according to the randomization protocol. For the fifth injection, all participants will receive the virtual reality technique. This design considers the injection as a statistical individual. A flow of participants in the study is in Table 1.

Table 1 : design of the study

	First injection	Second injection	Third injection	Fourth injection	Fifth injection
Group 1	Standard conditions	Control group	Control group	Control group	Virtual reality
Group 2	Standard conditions	Control group	Control group	Virtual reality	Virtual reality
Group 3	Standard conditions	Control group	Virtual reality	Virtual reality	Virtual reality

Participants

We will recruit participants from a cohort of patients receiving botulinum toxin injections on a regular basis in the Department of Physical Medicine and Rehabilitation at CHU Clermont-Ferrand. Participants will be included after assessing the inclusion and exclusion criteria (table 2) and will give

written consent within 1 month after the consultation. The duration of participation is 1 year for each participant.

Table 2 Eligibility criteria for participants

Inclusion criteria:	– adult, male or female, with spasticity of neurological origin (multiple sclerosis, cerebral stroke, traumatic brain injury etc.) and eligible for botulinum toxin injection – Able to deliver informed consent to participate in the study – Affiliation with a social security system
Exclusion criteria:	– Medical contraindication to virtual reality (epilepsy, schizophrenia, strabismus, amblyopia, anisometropia), local contraindication of wearing a mask (lesion of the face or the skull) – Major cognitive disorders – Any medical condition deemed by the investigator to be incompatible with the research – Indication of sedation by MEOPA (Mélange équimolaire oxygène protoxyde d'azote) during botulinum toxin injection sessions – Previously experienced virtual reality – Medical treatment or condition that may disturb heart rate variability – Pregnant or breastfeeding – Under guardianship or curatorship or safeguard of justice – Refusal to participate

Interventions

The DEEPSEN virtual reality mask will be worn in front of the eyes with the headphones on the ears during the entire consultation. The participant will remain on the examination table. The participant will choose the virtual reality scenario among five different scenarios. The mask can also be controlled by the investigator, who can stop the device at any moment.

No pain medication in addition to the participant's usual prescription will be allowed during the procedure.

During the injections, the same protocol will be used for each participant alone: echo-guided tracking technique or electrostimulation, MYOBOT needle, and ice analgesia for palmar or plantar injections.

Primary outcome

The primary outcome is the effect of virtual reality on stress (by HRV) (19,20) at rest, before, during and after botulinum toxin injection. HRV will be evaluated by the fluctuation degree of the duration of heart contractions or the interval between contractions assessed with a cardiofrequency meter.

Secondary outcomes

One secondary outcome is the effect of virtual reality during botulinum toxin injection on pain induced by the injection. The intensity of pain the patient experiences during botulinum toxin injection will be measured by a simple numerical scale ranging from 0 "no pain" to 10 "worst pain imaginable", immediately after the end of the session (21). 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".

STATISTICAL CONSIDERATIONS

Sample size estimation

To evaluate the effect of virtual reality on stress during botulinum toxin injection, the HRV criteria will be compared between randomization groups: virtual reality and control (virtual reality without sound and image). Using the log ratio of low frequency to high frequency (LF/HF) as an

evaluation criterion and considering the work of Dutheil et al. (19,20), 24 participants (patients as their own control) are required to demonstrate a clinically relevant difference of 0.2 for standard deviation 0.3, two-sided type 1 risk of error 5%, and power > 80%.

To take into account the specificities of the quasi-experimental design with sequential permutation and more precisely the intra-individual variability measured by the intra-class correlation coefficient, we will include 42 participants. The rate of lost to follow-up should be minimal or zero because this is a conventional care pathway.

Statistical analysis

All analysis will be performed with Stata 13 (StataCorp, College Station, TX, USA), and R (https://cran.r-project.org/) considering a risk of bilateral type 1 error 5%.

Baseline characteristics will be presented as mean ± SD or median (interquartile range) for continuous data (assumption of normality assessed by the Shapiro-Wilk test) and number (percentage) for categorical data. The following data will be collected: root mean square of successive differences between normal (RMSSD), SD of the normal sinus beats (SDNN), percentage of adjacent NN intervals that differ from each other by > 50 ms (pNN50), total power, and frequency-domain measurements to separate HRV into its component very LF (VLF), LF, LF/HF and HF rhythms that operate within different frequency ranges (22). The association between these variables will be analysed by correlation coefficient (Pearson or Spearman, according to statistical distribution) applying Sidak's type I error correction.

Regarding the data from HR monitoring, all devices will be uploaded to Bioharness Zephyr software. Analyses from Zephyr will involve using Kubios software. We will delete incorrect data due to artefacts by using a very-low filter in the Kubios software (23–27)

Participants will be described and compared between groups for inclusion according to eligibility criteria, epidemiological characteristics and clinical characteristics. We will also describe the protocol deviations, the distribution according to these deviations and the causes of lost to follow-up.

The initial comparability of the two groups will be assessed by the key characteristics of participants and potential factors associated with the primary outcome. A possible difference between the two groups on one of these characteristics will be determined according to clinical and statistical considerations.

Comparisons between groups will be systematic without adjustment, by adjusting for factors whose distribution could be unbalanced between groups despite randomization.

The main analysis will be intent-to-treat; a per-protocol analysis will be considered in a second step.

Primary analysis

The main objective of this study is to assess the effect of virtual reality on stress during botulinum toxin injection. According to the quasi-experimental design with sequential permutations, the main analysis will be based on a comparison of the primary outcome, pain during the injection, HRV during the first and last injection at each session by randomization groups with mixed models allowing to account for inter- and intra-individual and inter- and intra-injection variability (participant and injection considered random effects). The results will be expressed in terms of effect size and 95% confidence interval (CI).

Secondary analysis

In a second step, the possible confounding factors chosen in relation to the results of univariate analysis and their clinical relevance will be studied by multivariate analysis with a linear regression model. The normality of residues from these models will be studied. If necessary, the dependent variable can be transformed (logarithmic transformation). The results will be expressed in terms of effect sizes and 95% CI.

Secondary criteria of a quantitative nature (pain assessed by VAS (Visual Analogue Scale) during the injection and at the end of the procedure, and variation in pain and heart rate) will be studied according to the same analysis plan as described for the main outcome. As appropriate,

categorical variables will be compared by chi-square test or Fisher exact test on univariate analysis and mixed generalized linear regression on multivariate analysis. The results will be expressed in terms of absolute differences, odds ratios and 95% CIs.

To assess the technique addiction and the effect of repeated use, particular attention will be paid to the study of the randomization x injection group interaction evaluated as a fixed effect in the mixed models described above.

Subgroup analyses of factors likely to affect the primary endpoint will be considered after a study of subgroup x randomization group interaction by using a regression model.

A sensitivity analysis will be conducted to investigate the attrition bias of the quantity (level of attrition) and nature (independence from the randomization group) of missing data and to propose the most appropriate method of data imputation (maximum bias or multiple imputation).

ETHICS AND DISSEMINATION

All participants will receive oral and written information on the aim of the study and the protocol. Written informed consent will be obtained before their inclusion in the study and before performing any specific procedure. During the study, participants will have the opportunity to ask the investigator all questions concerning the protocol. They will be informed that they will be free to stop the study at any time at their own discretion, in accordance with Good Clinical Practice enforced under the French regulatory framework. Any adverse event that could occur during the protocol will be reported to the principal investigator. Should there be any negative impact of participating in the study on the participant's health status, the participant will be entitled to compensation in accordance with the French regulations.

Pursuant to the provisions concerning the confidentiality of data that are available to individuals responsible for quality control of biomedical research, individuals with direct access to the data will take all necessary precautions to ensure the confidentiality of information (identity and participant results). Data collected will be anonymized.

Participant and public involvement

Participants requiring botulinum toxin injection therapy will be recruited during rehabilitation consultations. In addition, participants will need to meet the inclusion and non-inclusion criteria described above (table 2) to participate in the study.

Data will be provided during the previous consultation (at least 1 month before the injection). Participants will be given sufficient time to think about inclusion before giving consent.

DISCUSSION

The aim of the study is to assess the effect of an immersive virtual reality on stress during botulinum toxin injection for spasticity in adults. The expected benefit for the patient is improving the tolerance of injections. The same research involved a pediatric population and showed that virtual reality was helpful in reducing botulinum injection-related discomfort in most children (3).

The design of this study can meet the highest level of evidence with its randomized quasi-experimental design and sequential permutations.

Virtual reality has multiple advantages because it is non-invasive and non-pharmacological, with low cost and easy accessibility and portability.

Although stress is an abstract notion, it can be expressed by HRV, which is sensitive to sympathomimetic influences and requires highly standardized conditions.

Authors' contributions:

The conception and design of the study was made by MB, IH, BP, MPV, EC. The drafting of the original protocol by MB, IH, BP, MPV, EC. The coordination of the study by IH, MPV, EC. The acquisition of data by MB, IH, BP, MPV, EC, PG, MB. The design of the statistical analysis plan by IH,

BP, EC. The drafting of the present manuscript by MB, IH, BP, MPV, EC. The funding obtaining by APP, EC. The final approval by MB, IH, BP, MPV, EC, PG, MB, APP.

Author's disclosure

The authors are solely responsible for the design and conduct of the study. They are also responsible for all the study analysis, the drafting and editing of manuscript and its final content.

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The funder is responsible for the additional costs of any supplies or examinations specifically required by the research protocol for the implementation of the research.

N/A for the award/grant number.

Competing interests statement

The authors have no conflict of interest.

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Word count: 3960

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	3	Date and version identifier	6
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	17
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	1-17
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	1-17

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2-3-5
	6b	Explanation for choice of comparators	2-3-4-5
Objectives	7	Specific objectives or hypotheses	2-3-4-5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	2-3-4-5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	8-9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-10-11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	10
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10-11
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NO
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10-11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	NO

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10-11
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10-11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	NO
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	NO
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	17
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NO
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	7
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	5
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	NO

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	16-17
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NO
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NO
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	NO
	31b	Authorship eligibility guidelines and any intended use of professional writers	1
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NO
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	YES
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NO

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Use of immersive virtual reality for stress reduction during botulinum toxin injection for spasticity (RVTOX), a study protocol of a randomized control trial

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Use of immersive virtual reality for stress reduction during botulinum toxin injection for spasticity (RVTOX), a study protocol of a randomized control trial

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ABSTRACT

Introduction

Botulinum toxin injection is a common way to help reduce spasticity in the body caused by central neurological damage such as cerebral stroke, multiple sclerosis or traumatic brain injury. The pain felt during the injection causes most patients to experience significant stress for further injections, the level of which is variable between patients.

Immersive virtual reality is a digital technique that simulates the 3D spatial and sound environment around a person said to be immersed in this virtualized world. The effectiveness of virtual reality comes from the intensity of this multisensory immersion, known as the feeling of presence (i.e., subjective experience of being in one place or one environment, even when you are physically in another one).

Only one research article in pediatrics has shown that immersive reality technique has a positive impact on the level of pain and agitation suffered during botulinum toxin injections. None has been found dealing with applications on adults.

The purpose of this study is therefore to evaluate with sufficient assurance the following research hypothesis: Virtual reality can help adults cope with the stress and pain of botulinum toxin treatment injection.

Methods and analysis

The research hypothesis will be tested using a randomized stepped wedge method versus a non-invasive technique (headset with virtual reality session) to its control (headset with no image nor audio).

For the patient population under test, a first injection session will be carried out without adding any particular device. During the second injection session, all patients will receive the control technique. Patients will then receive either the control technique or the virtual reality technique, depending on the randomization plan. Finally, at the 5th injection, all patients will receive the virtual reality technique. Such a design leads to considering the injection as a statistical unit as all participants will undergo the standard condition, the control technique and virtual reality technique.

Ethics and dissemination

Patients will be fully and fairly informed in terms of their understanding of the objectives and constraints of the study and the possible risks involved. They will also be entitled to refuse the study and/or withdraw and this refusal will have no impact on their follow-up as part of their pathology. In addition, the investigator will inform the subjects of the opinion given by the people protection committee.

Ethics were approved by the Comité de Protection des Personnes Nord-Ouest in January 2022

ClinicalTrials.gov: NCT05364203

Date and version of the protocol: Version 2 of the protocol 08/03/2022

Keywords: Virtual Reality Therapy, stress disorder, pain, muscle spasticity, botulinum toxins.

Strengths and limitation of this study

- This study will be the first to assess the effects of an immersive virtual reality on stress during injections of botulinum toxin in spasticity in adults.
- 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.
- The design of this study tends to meet the highest level of evidence.
- Stress is an abstract notion and there are no references for its evaluation, but it will be studied through heart rate variability.
- The effect might be modest for patient who receive injections from many years, due to a habituation effect.

INTRODUCTION

The effectiveness of botulinum toxin injections on spasticity has been widely demonstrated in brain lesions(1). This treatment is therefore used in many patients with central neurological deficit (stroke, multiple sclerosis, spinal cord injury, traumatic brain injury). Unfortunately, as the effect of botulinum toxin is temporary (approximately 3 months), these intramuscular injections must be repeated every 3 to 4 months. The tolerance of the injections varies from one patient to another. The pain felt during the injection depends at first on the technique used (electrical stimulation) and the body site where the injection is made (palm and plantar injections are the most painful sites) and secondarily due to the skin break-in (2). Unfortunatly, most patients experience significant stress during the injection.

Concerning botulinum toxin, it has been shown that this toxin, by intramuscular injection, exerts a decrease in hypertonia (1). In fact, botulinum toxin has been a reference treatment for focal spasticity since the recommendations of the ANSM of 2011. One study specifically studied the effect of virtual reality on pain during botulinum toxin injection in pediatrics.(3)

Various reactions of the body caused by stress are known to be related to the change of autonomic nervous system, and stress can be assessed objectively using biomarkers, and heart rate variability (HRV).(4) Heart rate can be measured non-invasively, is painless, easy to use, and reproducible(5). It reflects the cardiovascular response to regulatory impulses affecting heart rhythm (6). In general, heart rate variability is a reliable indicator of autonomic nervous system activity(9), and many previous studies have used heart rate variability for mental stress estimation (7–10)

Immersive virtual reality is a digital technique that simulates the 3D spatial and sound environment around a person said to be immersed in this virtualized world. 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 (11). There is solid evidence from controlled research that virtual reality distraction is effective for reducing experimental pain, as well as the pain associated with burn injury care(12). 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.(13)

Several studies focused on the effectiveness of virtual reality in recent years to reduce pain in various painful medical procedures,(14) reduction of pain in the treatment of burn injuries thanks to a virtual reality system(12,15,16), and pain reduction during episiotomy repair using a virtual reality system(17). The influence of patients' clinical characteristics on pain during botulinum toxin injections has been studied by Mathevon(2). Use of virtual reality in hospitalized patients significantly reduces pain versus a control distraction condition. These results indicate that virtual reality is an effective and safe adjunctive therapy for pain management in the acute inpatient setting(16).

The only published study on pain felt during botulinum injections concern the effect of the tracking technique. No studies have yet evaluated the effect of techniques to reduce stress and pain during injection in adults. The only publication concerns the pediatric population and shows decrease of pain and agitation during botulinum injections using virtual reality.(3)

Therefore, the hypothesis of this research is that an immersive virtual reality system can, in adults, reduce the stress and painful experience of botulinum toxin injections. The aim of the study is to evaluate the effect of virtual reality on stress induced by botulinum toxin injections.

METHODS AND ANALYSIS

Trial design

It is a stepped wedged randomized controlled clinical trial, single blinded as only the investigator will be blinded.

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) (i) those with a first injection in control condition (virtual reality headset with no image nor audio) and then three injections in virtual reality condition (headset with virtual reality session), (ii) those with two first injections in control condition and then two injections in virtual reality condition and (iii) those with three first injections in control condition and then one injection in virtual reality condition.

The design of this trial will adhere to the requirements of the Standard Protocol Items: Recommendations for Interventional Trials (Supplemental material for editors only). The results will be reported in accordance with the CONSORT Statement for non-pharmacologic trials.

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 to measure the efficacy after several injections, to study the between and within patient variability and to increase the statistical power. A flow of the participants through the study is provided in Table 1.

Table 1: design of the study

	First injection	**Second injection**	**Third injection**	**Fourth injection**	**Fifth injection**
Step 1	Standard conditions	Control group	Control group	Control group	Virtual reality
Step 2	Standard conditions	Control group	Control group	Virtual reality	Virtual reality

Step 3	Standard conditions	Control group	Virtual reality	Virtual reality	Virtual reality

Participants

We will recruit patients from a cohort of patient treated on a regular basis with botulinum toxin injections in Clermont-Ferrand University Hospital in the department of Physical Medicine and Rehabilitation. The recruitment will go from May 10, 2022 until October 30, 2024. Patients will have to respond to the inclusion and exclusion criteria listed below (table 2) and give written consent within one month after the consultation. The duration of participation in the study is one year for each patient.

Table 2 Eligibility criteria for participants

Inclusion criteria:	– adult, male or female, with spasticity of neurological origin (multiple sclerosis, cerebral stroke, traumatic brain injury etc.) and eligible for botulinum toxin injection – Able to deliver informed consent to participate in the study – Affiliation with a social security system
Exclusion criteria:	– Medical contraindication to virtual reality (epilepsy, schizophrenia, strabismus, amblyopia, anisometropia), local contraindication of wearing a headset (dermatological lesion of the face or the skull) – Any medical condition deemed by the investigator to be incompatible with the research (eg : major cognitive disorders MMS < 24/30, impaired vision or hearing) – Indication of sedation by ENTONOX during botulinum toxin injection sessions – Every patient who has experienced virtual reality – Cardiovascular diagnosis of rhythm perturbances or priorly diagnosed anxiety disorders that may inder results – Pregnant or breastfeeding women

Interventions

DEEPSEN virtual reality headset will be worn during the entire time of the consultation in front of the eyes, the headphones on the ears. The patient will have to stay on the examination table. 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 balloon). The headset can also be controlled by the therapist who can stop at any moment the device, and the device will be disinfected between each participant.

No pain medication in addition to the patient's usual prescription will be allowed during the procedure.

During the injections, the same protocol will be used each time for each patient alone: echo-guided tracking technique or electrostimulation, MYOBOT needle, ice analgesia for palmar or plantar injections.

Primary outcome

The primary outcome is the effect of virtual reality on stress (by HRV) (18,19) at rest, before, during and after botulinum toxin injection. HRV will be evaluated by the fluctuation degree of the duration of heart contractions or the interval between contractions assessed with a heart rate monitor.

Secondary outcomes

One secondary outcome is the effect of virtual reality during botulinum toxin injection on pain induced by the injection. The intensity of pain during botulinum toxin injection will be measured by a simple numerical scale ranging from 0 “no pain” to 10 “worst pain imaginable”, immediately after the end of the session.

STATISTICAL CONSIDERATIONS

Sample size estimation

In order to evaluate the effect of virtual reality on stress during botulinum toxin injections, the HRV will be compared between groups, virtual reality vs. control group (virtual reality headset without sound and image). 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 1 error of 5%, and a statistical power greater than 80%, according to the results reported by Dutheil and al (18,19).

Due to the 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 be negligible, 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 (SD) 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 based on clinical and statistical considerations. The type 1 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 then be 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 bases on a comparison of the primary endpoint (heart rate variability) between groups (control vs.

Virtual reality) by random-effects model considering 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 analysis

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 analysis 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).

Regarding the data from HR monitoring, all devices will be uploaded with Bioharness Zephyr software. Analysis from Zephyr will involve Kubios software. We will delete incorrect data due to artefacts using very-low filter in the Kubios software (20–24)

ETHICS AND DISSEMINATION

Ethics were approved by the Comité de Protection des Personnes Nord-Ouest in January 2022 . All participants will receive oral and written information on the aim of the study and the protocol. Written informed consent will be obtained before their inclusion in the study and before performing any specific procedure. During the study, participants will have the opportunity to ask the investigator all questions concerning the protocol. They will be informed that they will be free to stop the study at any time at their own discretion, in accordance with Good Clinical Practice enforced under the French regulatory framework. Any adverse event that could occur during the protocol will be reported to the principal investigator. Should there be any negative impact of participating in the study on the participant's health status, the participant will be entitled to compensation in accordance with the French regulations.

Pursuant to the provisions concerning the confidentiality of data that are available to individuals responsible for quality control of biomedical research, individuals with direct access to the data will take

all necessary precautions to ensure the confidentiality of information (identity and participant results). Data collected will be anonymized.

Participant and public involvement

Patients were not involved in the design and planning of the study. The information will be provided during the previous consultation (at least one-month before the injection). Patients will be given sufficient time to think about inclusion before giving consent.

DISCUSSION

Both immersion and involvement are necessary for experiencing presence and they interact to determine how much presence is reported (25). Virtual reality has multiple advantages because it is non-invasive and non-pharmacological, with low cost and easy accessibility and portability. 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 (11). There is solid evidence from controlled research that virtual reality distraction is effective for reducing experimental pain (12). Our study aims to assess the effects of an immersive virtual reality on stress during botulinum toxin injections in spasticity in adults. The expected benefit for the patient is improving the tolerance of injections. The same research involved a pediatric population and showed that virtual reality was helpful in reducing botulinum injection-related discomfort in most children (3).

Although stress is an abstract notion, it can be expressed by HRV, which is sensitive to sympathomimetic influences and requires highly standardized conditions. In general, HRV is a reliable indicator of autonomic nervous system activity (26), and many previous studies have used heart rate variability for mental stress estimation (7–9).

Yet, a few limitations that might be interesting to cite is first the tolerance of virtual reality. It might be different from a patient to another, and might be responsible for lost to follow up, for example due to nausea during viewing. But the number of patients needed to be included was calculated

accordingly. Another limitation might be an habituation effect with less stress for patients who receive this therapy since a few years.

Authors' contributions:

The conception and design of the study was made by MB, IH, BP, MPV, EC. The drafting of the original protocol by MB, IH, BP, MPV, EC. The coordination of the study by IH, MPV, EC. The acquisition of data by MB, IH, BP, MPV, EC, PG, MB. The design of the statistical analysis plan by IH, BP, EC. The drafting of the present manuscript by MB, IH, BP, MPV, CL, EC, CO. The funding obtaining by APP, EC. The final approval by MB, IH, BP, MPV, EC, PG, MB, CL, APP.

Author's disclosure

The authors are solely responsible for the design and conduct of the study. They are also responsible for all the study analysis, the drafting and editing of manuscript and its final content.

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The promotor is responsible for the additional costs of any supplies or examinations specifically required by the research protocol for the implementation of the research.

Award/grant number : NA

Competing interests statement : none

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Word count: 2724

DESCRIPTIFS CONTENUS DISPOSITIFS VRx

Camargue : Bord de mer, dunes de sable, vent dans les roseaux, flamands rose, chevaux.
Contenu destiné à la sédation et l'analgésie.

Montagne en été : Rivière, cascade, lac, promenade sur le thème de l'eau et ses bienfaits.
Contenu lent et statique destiné à la sédation et l'analgésie.

Montagne en hiver : La pureté du blanc, l'immobilité que confère la neige à toutes choses.
Contenu lent et statique destiné à la sédation et l'analgésie.

Spitzberg : Paysage de glace, navigation à bord d'un voilier au milieu de la banquise avec présence de personnes.
Contenu destiné à la sédation et l'analgésie.

Pique-nique en montagne : Promenade automnale dans les Alpes autour d'un chalet et d'un pique-nique.
Contenu calme destiné à la sédation.

Inde : Voyage entre les villes, les campagnes et les temps colorés d'Inde avec parfois la présence de personne.
Contenu lent et statique destiné à la sédation et l'analgésie.
Prévenir de la sensation de vertige.

Montgolfière : Voyage en montgolfière avec le Mont Blanc au loin, du décollage à l'atterrissage.
Contenu destiné à la sédation et l'analgésie forte.
Prévenir de la sensation de vertige.

Au fil de l'eau : Descente d'une rivière calme à bord d'un canoë, bercé par un mouvement de balancier.
Contenu destiné à la sédation forte et l'analgésie
Prévenir du risque du mal des transports

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	3	Date and version identifier	6
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	17
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	1-17
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	1-17

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2-3-5
	6b	Explanation for choice of comparators	2-3-4-5
Objectives	7	Specific objectives or hypotheses	2-3-4-5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	2-3-4-5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	8-9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-10-11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	10
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10-11
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NO
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10-11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	NO

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10-11
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10-11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	NO
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	NO
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	17
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NO
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	7
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	5
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	NO

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	16-17
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NO
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NO
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	NO
	31b	Authorship eligibility guidelines and any intended use of professional writers	1
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NO
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	YES
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NO

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Use of immersive virtual reality for stress reduction during botulinum toxin injection for spasticity (RVTOX), a study protocol of a randomized control trial

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Use of immersive virtual reality for stress reduction during botulinum toxin injection for spasticity (RVTOX), a study protocol of a randomized control trial

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ABSTRACT

Introduction

Botulinum toxin injection is a common way to help reduce spasticity in the body caused by central neurological damage such as cerebral stroke, multiple sclerosis or traumatic brain injury. The pain felt during the injection causes most patients to experience significant stress for further injections, the level of which is variable between patients.

Immersive virtual reality is a digital technique that simulates the 3D spatial and sound environment around a person said to be immersed in this virtualized world. The effectiveness of virtual reality comes from the intensity of this multisensory immersion, known as the feeling of presence (i.e., subjective experience of being in one place or one environment, even when you are physically in another one).

Only one research article in pediatrics has shown that immersive reality technique has a positive impact on the level of pain and agitation suffered during botulinum toxin injections. The purpose of this study is therefore to evaluate with sufficient assurance the following research hypothesis: Virtual reality can help adults cope with the stress and pain of botulinum toxin treatment injection.

Methods and analysis

The research hypothesis will be tested using a randomized stepped wedge method versus a non-invasive technique (headset with virtual reality session) to its control (headset with no image nor audio).

The design leads to considering the injection as a statistical unit as all participants will undergo the standard condition, the control technique and virtual reality technique.

Ethics and dissemination

Patients will be fully and fairly informed in terms of their understanding of the objectives and constraints of the study and the possible risks involved. They will also be entitled to refuse the study and/or withdraw and this refusal will have no impact on their follow-up as part of their pathology. Dissemination of the results of this study will be through peer-reviewed publications, and national and international conferences.

Ethics were approved by the Comité de Protection des Personnes Nord-Ouest in January 2022.

ClinicalTrials.gov: NCT05364203

Date and version of the protocol: Version 2 of the protocol 08/03/2022

Keywords: Virtual Reality Therapy, stress disorder, pain, muscle spasticity, botulinum toxins.

Strengths and limitation of this study

- This study will be the first to assess the effects of an immersive virtual reality on stress during injections of botulinum toxin in spasticity in adults.
- 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.
- The design of this study tends to meet the highest level of evidence.
- Stress is an abstract notion and there are no references for its evaluation, but it will be studied through heart rate variability.
- The effect might be modest for patient who receive injections from many years, due to a habituation effect.

INTRODUCTION

The effectiveness of botulinum toxin injections on spasticity has been widely demonstrated in brain lesions(1). This treatment is therefore used in many patients with central neurological deficit (stroke, multiple sclerosis, spinal cord injury, traumatic brain injury). Unfortunately, as the effect of botulinum toxin is temporary (approximately 3 months), these intramuscular injections must be repeated every 3 to 4 months. The tolerance of the injections varies from one patient to another. The pain felt during the injection depends at first on the technique used (electrical stimulation) and the body site where the injection is made (palm and plantar injections are the most painful sites) and secondarily due to the skin break-in (2). Unfortunatly, most patients experience significant stress during the injection.

Concerning botulinum toxin, it has been shown that this toxin, by intramuscular injection, exerts a decrease in hypertonia (1). In fact, botulinum toxin has been a reference treatment for focal spasticity since the recommendations of the ANSM of 2011. One study specifically studied the effect of virtual reality on pain during botulinum toxin injection in pediatrics.(3)

Various reactions of the body caused by stress are known to be related to the change of autonomic nervous system, and stress can be assessed objectively using biomarkers, and heart rate variability (HRV).(4) Heart rate can be measured non-invasively, is painless, easy to use, and reproducible(5). It reflects the cardiovascular response to regulatory impulses affecting heart rhythm (6). In general, heart rate variability is a reliable indicator of autonomic nervous system activity(9), and many previous studies have used heart rate variability for mental stress estimation (7–10)

Immersive virtual reality is a digital technique that simulates the 3D spatial and sound environment around a person said to be immersed in this virtualized world. 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 (11). There is solid evidence from controlled research that virtual reality distraction is effective for reducing experimental pain, as well as the pain associated with burn injury care(12). 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.(13)

Several studies focused on the effectiveness of virtual reality in recent years to reduce pain in various painful medical procedures,(14) reduction of pain in the treatment of burn injuries thanks to a virtual reality system(12,15,16), and pain reduction during episiotomy repair using a virtual reality system(17). The influence of patients' clinical characteristics on pain during botulinum toxin injections has been studied by Mathevon(2). Use of virtual reality in hospitalized patients significantly reduces pain versus a control distraction condition. These results indicate that virtual reality is an effective and safe adjunctive therapy for pain management in the acute inpatient setting(16).

The only published study on pain felt during botulinum injections concern the effect of the tracking technique. No studies have yet evaluated the effect of techniques to reduce stress and pain during injection in adults. The only publication concerns the pediatric population and shows decrease of pain and agitation during botulinum injections using virtual reality.(3)

Therefore, the hypothesis of this research is that an immersive virtual reality system can, in adults, reduce the stress and painful experience of botulinum toxin injections. The aim of the study is to evaluate the effect of virtual reality on stress induced by botulinum toxin injections.

METHODS AND ANALYSIS

Trial design

It is a stepped wedged randomized controlled clinical trial, single blinded as only the investigator will be blinded.

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) (i) those with a first injection in control condition (virtual reality headset with no image nor audio) and then three injections in virtual reality condition (headset with virtual reality session), (ii) those with two first injections in control condition and then two injections in virtual reality condition and (iii) those with three first injections in control condition and then one injection in virtual reality condition.

The design of this trial will adhere to the requirements of the Standard Protocol Items: Recommendations for Interventional Trials (supplemental material 1). The results will be reported in accordance with the CONSORT Statement for non-pharmacologic trials.

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 to measure the efficacy after several injections, to study the between and within patient variability and to increase the statistical power. A flow of the participants through the study is provided in Table 1.

Table 1: design of the study

	First injection	Second injection	Third injection	Fourth injection	Fifth injection
Step 1	Standard conditions	Control group	Control group	Control group	Virtual reality
Step 2	Standard conditions	Control group	Control group	Virtual reality	Virtual reality

Step 3	Standard conditions	Control group	Virtual reality	Virtual reality	Virtual reality

Participants

We will recruit patients from a cohort of patient treated on a regular basis with botulinum toxin injections in Clermont-Ferrand University Hospital in the department of Physical Medicine and Rehabilitation. The recruitment will go from May 10, 2022 until October 30, 2024. Patients will have to respond to the inclusion and exclusion criteria listed below (table 2) and give written consent within one month after the consultation. The duration of participation in the study is one year for each patient.

Table 2 Eligibility criteria for participants

Inclusion criteria:	– adult, male or female, with spasticity of neurological origin (multiple sclerosis, cerebral stroke, traumatic brain injury etc.) and eligible for botulinum toxin injection – Able to deliver informed consent to participate in the study – Affiliation with a social security system
Exclusion criteria:	– Medical contraindication to virtual reality (epilepsy, schizophrenia, strabismus, amblyopia, anisometropia), local contraindication of wearing a headset (dermatological lesion of the face or the skull) – Any medical condition deemed by the investigator to be incompatible with the research (eg : major cognitive disorders MMS < 24/30, impaired vision or hearing) – Indication of sedation by ENTONOX during botulinum toxin injection sessions – Every patient who has experienced virtual reality – Cardiovascular diagnosis of rhythm perturbances or priorly diagnosed anxiety disorders that may inder results – Pregnant or breastfeeding women

Interventions

DEEPSEN virtual reality headset will be worn during the entire time of the consultation in front of the eyes, the headphones on the ears. The patient will have to stay on the examination table. Virtual reality scenario is chosen by the patient between 8 different scenarios (supplemental material 2 : dunes landscape, mountain during summer or winter, Spitzberg landscape on a boat, mountain picnic in the Alpes, countryside in India, river and air balloon). The headset can also be controlled by the therapist who can stop at any moment the device, and the device will be disinfected between each participant.

No pain medication in addition to the patient's usual prescription will be allowed during the procedure.

During the injections, the same protocol will be used each time for each patient alone: echo-guided tracking technique or electrostimulation, MYOBOT needle, ice analgesia for palmar or plantar injections.

Primary outcome

The primary outcome is the effect of virtual reality on stress (by HRV) (18,19) at rest, before, during and after botulinum toxin injection. HRV will be evaluated by the fluctuation degree of the duration of heart contractions or the interval between contractions assessed with a heart rate monitor.

Secondary outcomes

One secondary outcome is the effect of virtual reality during botulinum toxin injection on pain induced by the injection. The intensity of pain during botulinum toxin injection will be measured by a simple numerical scale ranging from 0 “no pain” to 10 “worst pain imaginable”, immediately after the end of the session.

STATISTICAL CONSIDERATIONS

Sample size estimation

In order to evaluate the effect of virtual reality on stress during botulinum toxin injections, the HRV will be compared between groups, virtual reality vs. control group (virtual reality headset without sound and image). 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 1 error of 5%, and a statistical power greater than 80%, according to the results reported by Dutheil and al (18,19).

Due to the 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 be negligible, 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 (SD) 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 based on clinical and statistical considerations. The type 1 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 then be 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 bases on a comparison of the primary endpoint (heart rate variability) between groups (control vs.

Virtual reality) by random-effects model considering 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 analysis

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 analysis 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).

Regarding the data from HR monitoring, all devices will be uploaded with Bioharness Zephyr software. Analysis from Zephyr will involve Kubios software. We will delete incorrect data due to artefacts using very-low filter in the Kubios software (20–24)

ETHICS AND DISSEMINATION

Ethics were approved by the Comité de Protection des Personnes Nord-Ouest in January 2022 . All participants will receive oral and written information on the aim of the study and the protocol. Written informed consent will be obtained before their inclusion in the study and before performing any specific procedure. During the study, participants will have the opportunity to ask the investigator all questions concerning the protocol. They will be informed that they will be free to stop the study at any time at their own discretion, in accordance with Good Clinical Practice enforced under the French regulatory framework. Any adverse event that could occur during the protocol will be reported to the principal investigator. Should there be any negative impact of participating in the study on the participant's health status, the participant will be entitled to compensation in accordance with the French regulations.

According to the provisions concerning data confidentiality that are available to those responsible for the quality control of biomedical research, all researchers with direct access to the data will take the necessary precautions to ensure the confidentiality of information (participant identification

and results). All data collected will be anonymized. Our study will be continued by the investigator and a second article with the results will be published. Dissemination of the results of this study will be through peer-reviewed publications, and national and international conferences

Participant and public involvement

Patients were not involved in the design and planning of the study. The information will be provided during the previous consultation (at least one-month before the injection). Patients will be given sufficient time to think about inclusion before giving consent.

DISCUSSION

Both immersion and involvement are necessary for experiencing presence and they interact to determine how much presence is reported (25). Virtual reality has multiple advantages because it is non-invasive and non-pharmacological, with low cost and easy accessibility and portability. 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 (11). There is solid evidence from controlled research that virtual reality distraction is effective for reducing experimental pain (12). Our study aims to assess the effects of an immersive virtual reality on stress during botulinum toxin injections in spasticity in adults. The expected benefit for the patient is improving the tolerance of injections. The same research involved a pediatric population and showed that virtual reality was helpful in reducing botulinum injection-related discomfort in most children (3).

Although stress is an abstract notion, it can be expressed by HRV, which is sensitive to sympathomimetic influences and requires highly standardized conditions. In general, HRV is a reliable indicator of autonomic nervous system activity (26), and many previous studies have used heart rate variability for mental stress estimation (7–9).

Yet, a few limitations that might be interesting to cite is first the tolerance of virtual reality. It might be different from a patient to another, and might be responsible for lost to follow up, for example due to nausea during viewing. But the number of patients needed to be included was calculated accordingly. Another limitation might be an habituation effect with less stress for patients who receive this therapy since a few years.

Authors' contributions:

The conception and design of the study was made by MB, IH, BP, MPV, EC. The drafting of the original protocol by MB, IH, BP, MPV, EC. The coordination of the study by IH, MPV, EC. The acquisition of data by MB, IH, BP, MPV, EC, PG, MB. The design of the statistical analysis plan by IH, BP, EC. The drafting of the present manuscript by MB, IH, BP, MPV, CL, EC, CO. The funding obtaining by APP, EC. The final approval by MB, IH, BP, MPV, EC, PG, MB, CL, APP.

Author's disclosure

The authors are solely responsible for the design and conduct of the study. They are also responsible for all the study analysis, the drafting and editing of manuscript and its final content. The datasets analyzed during the current study and statistical code are available from the corresponding author on reasonable request, as is the full protocol.

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The promotor is responsible for the additional costs of any supplies or examinations specifically required by the research protocol for the implementation of the research.

Award/grant number : NA

Competing interests statement : none

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SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	3	Date and version identifier	6
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	17
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	1-17
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	1-17

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2-3-5
	6b	Explanation for choice of comparators	2-3-4-5
Objectives	7	Specific objectives or hypotheses	2-3-4-5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	2-3-4-5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	8-9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-10-11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	10
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10-11
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NO
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10-11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	NO

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10-11
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10-11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	NO
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	NO
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	17
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NO
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	7
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	5
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	NO

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	16-17
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NO
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NO
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	NO
	31b	Authorship eligibility guidelines and any intended use of professional writers	1
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NO
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	YES
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NO

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

DESCRIPTIFS CONTENUS DISPOSITIFS VRx

Camargue : Bord de mer, dunes de sable, vent dans les roseaux, flamands rose, chevaux.
Contenu destiné à la sédation et l'analgésie.

Montagne en été : Rivière, cascade, lac, promenade sur le thème de l'eau et ses bienfaits.
Contenu lent et statique destiné à la sédation et l'analgésie.

Montagne en hiver : La pureté du blanc, l'immobilité que confère la neige à toutes choses.
Contenu lent et statique destiné à la sédation et l'analgésie.

Spitzberg : Paysage de glace, navigation à bord d'un voilier au milieu de la banquise avec présence de personnes.
Contenu destiné à la sédation et l'analgésie.

Pique-nique en montagne : Promenade automnale dans les Alpes autour d'un chalet et d'un pique-nique.
Contenu calme destiné à la sédation.

Inde : Voyage entre les villes, les campagnes et les temps colorés d'Inde avec parfois la présence de personne.
Contenu lent et statique destiné à la sédation et l'analgésie.
Prévenir de la sensation de vertige.

Montgolfière : Voyage en montgolfière avec le Mont Blanc au loin, du décollage à l'atterrissage.
Contenu destiné à la sédation et l'analgésie forte.
Prévenir de la sensation de vertige.

Au fil de l'eau : Descente d'une rivière calme à bord d'un canoë, bercé par un mouvement de balancier.
Contenu destiné à la sédation forte et l'analgésie
Prévenir du risque du mal des transports