



Clinical Study Protocol (University Master's degree thesis in medicine)

IMPACT OF COMMUNICATION ON PAIN DURING INTRAVENOUS CANNULATION IN AN EMERGENCY DEPARTMENT: A RANDOMISED CONTROLLED TRIAL

Discomfort during the insertion of a peripheral intravenous catheter in an Emergency Department: impact of communication

Study Type: Other Clinical Trials (ClinO Chapter 4)

Study Categorisation: A (ClinO Art. 61)

Study Registration: Registration on the FOPH's SNCTP and clinicaltrials.gov once the study has been approved by the CEC

Study Identifier: Non-applicable

Sponsor, Principal Investigator, Co-investigators: Sponsor: Lausanne University Hospital (LUH), Lausanne, Switzerland
Principal Investigator, Sponsor: Dr O. Hugli, MD, MPH, Emergency Department, LUH, Lausanne, Switzerland
Co-investigator, Co-sponsor: Dre C. Berna, MD-PhD, Antalgia Center, Anesthesiology Department, LUH, Lausanne, Switzerland
Co-investigator: Anne Beyeler, 1st year M.A. Medical Student, UNIL, Lausanne, Switzerland
Co-investigator: Adélaïde Le Bloc'h, 1st year M.A. Medical Student, UNIL, Lausanne, Switzerland
Co-investigator: Hélène Gerhard-Donnet, research nurse, Emergency Department, LUH, Lausanne, Switzerland

Investigational Product: Clinical communication

Protocol Version and Date: Version 2, Septembre 27. 2017

Table of Contents

STUDY SYNOPSIS	5
ABBREVIATIONS	10
STUDY SCHEDULE	11
1. STUDY ADMINISTRATIVE STRUCTURE	12
1.1 Sponsor, Principal Investigator	12
1.2 Co-investigators	12
1.3 Statistician ("Biostatistician")	12
1.4 Laboratory	12
1.5 Monitoring institution	12
1.6 Data Safety Monitoring Committee	12
1.7 Any other relevant Committee, Person, Organisation, Institution	12
2. ETHICAL AND REGULATORY ASPECTS	13
2.1 Study registration	13
2.2 Categorisation of study	13
2.3 Competent Ethics Committee (CEC)	13
2.4 Competent Authorities (CA)	13
2.5 Ethical Conduct of the Study	13
2.6 Declaration of interest	13
2.7 Patient Information and Informed Consent	13
2.8 Participant privacy and confidentiality	14
2.9 Early termination of the study	14
2.10 Protocol amendments	14
3. BACKGROUND AND RATIONALE	15
3.1 Background and Rationale	15
3.2 Investigational Product (treatment, device) and Indication	15
3.3 Preclinical Evidence	16
3.4 Clinical Evidence to Date	16
3.5 Dose Rationale / Medical Device: Rationale for the intended purpose in study (pre-market MD)	16
3.6 Explanation for choice of comparator (or placebo)	16
3.7 Risks / Benefits	16
3.8 Justification of choice of study population	17
4. STUDY OBJECTIVES	18
4.1 Overall Objective	18
4.2 Primary Objective	18
4.3 Secondary Objectives	18
4.4 Safety Objectives	18
5. STUDY OUTCOMES	19
5.1 Primary Outcomes	19
5.2 Secondary Outcomes	19
5.3 Safety Outcomes	19
6. STUDY DESIGN	20
6.1 General study design and justification of design	20
6.2 Methods of minimising bias	21
6.2.1 Randomisation	21
6.2.2 Blinding procedures	21

6.2.3	Other methods of minimising bias.....	21
6.3	Unblinding Procedures (Code break).....	22
7.	STUDY POPULATION	23
7.1	Eligibility criteria	23
7.2	Recruitment and screening	23
7.3	Assignment to study groups.....	23
7.4	Criteria for withdrawal / discontinuation of participants.....	23
8.	STUDY INTERVENTION	25
8.1	Identity of Investigational Products	25
8.1.1	Experimental Intervention	25
8.1.2	Control Intervention.....	25
8.1.3	Packaging, Labelling and Supply (re-supply)	25
8.1.4	Storage Conditions.....	25
8.2	Administration of experimental and control interventions	26
8.3	Dose / Device modifications.....	26
8.4	Compliance with study intervention	26
8.5	Data Collection and Follow-up for withdrawn participants	26
8.6	Trial specific preventive measures.....	26
8.7	Concomitant Interventions (treatments).....	26
8.8	Study Drug / Medical Device Accountability	26
8.9	Return or Destruction of Study Drug / Medical Device	26
9.	STUDY ASSESSMENTS.....	27
9.1	Study flow chart(s) / table of study procedures and assessments	27
9.2	Assessments of outcomes	27
9.2.1	Assessment of primary and secondary outcomes	27
9.2.2	Assessment of safety outcomes	27
9.2.3	Assessments in participants who prematurely stop the study	28
9.3	Procedures at each visit.....	28
10.	SAFETY	29
11.	STATISTICAL METHODS.....	30
11.1	Hypothesis.....	30
11.2	Determination of Sample Size.....	30
11.3	Statistical criteria of termination of trial	30
11.4	Planned Analyses.....	30
11.4.1	Datasets to be analysed, analysis populations.....	30
11.4.2	Primary Analysis	30
11.4.3	Secondary Analyses	30
11.4.4	Interim analyses	31
11.4.5	Safety analysis	31
11.4.6	Deviation(s) from the original statistical plan	31
11.5	Handling of missing data and drop-outs.....	31
12.	QUALITY ASSURANCE AND CONTROL.....	32
12.1	Data handling and record keeping / archiving.....	32
12.1.1	Case Report Forms.....	32
12.1.2	Specification of source documents	32
12.1.3	Record keeping / archiving	32

12.2	Data management.....	32
12.3	Monitoring.....	32
12.4	Audits and Inspections	33
12.5	Confidentiality, Data Protection	33
12.6	Storage of biological material and related health data.....	33
13.	PUBLICATION AND DISSEMINATION POLICY.....	34
14.	FUNDING AND SUPPORT.....	34
15.	INSURANCE.....	34
16.	REFERENCES.....	35
17.	APPENDICES.....	38

STUDY SYNOPSIS

Sponsor / Sponsor- Investigator:	Sponsor: Lausanne University Hospital (LUH), Lausanne, Switzerland Principal Investigator, Sponsor: Dr O. Hugli, MD, MPH, Emergency Department, LUH, Lausanne, Switzerland
Study Title:	Impact of communication on pain during intravenous cannulation in an Emergency Department: a randomised controlled trial
Short Title:	Discomfort during the insertion of a peripheral intravenous catheter in an Emergency Department: impact of communication
Protocol Version and Date:	Version 2, Septembre 27. 2017
Trial registration:	Registration on the Federal Office of Public Health (FOPH) Swiss National Clinical Trials Portal (SNCTP) and clinicaltrials.gov once the study has been approved by the CEC
Study category and Rationale:	This randomized clinical trial addresses the modulation of the information given to Emergency Department (ED) patients prior to a peripheral intravenous catheter (PIC) insertion. The study compares the impact on pain and anxiety of a standard information message or a message with positive content when a PIC is placed. This intervention only entails a very brief information, relating to a medically required procedural procedure and therefore involves minimal risks for the patients. The constraints are also minimal since the participation of patients, in parallel with a procedure necessary for their clinical management, will be unique and limited in time. It is therefore a risk category A study.
Clinical Phase:	Non applicable
Background and Rationale:	The occurrence of a medical or surgical emergency is a stressful life event. An Emergency Department (ED) is also a noisy and sometimes chaotic environment, contributing in itself to increase anxiety associated with the reason for consultation. Some common medical procedures, such as PIC insertion, can not only induce pain, but can also exacerbate anxiety or pre-existing pain. Nevertheless, the well-being of patients, especially during invasive medical procedures, can be improved by various communication techniques. However, the literature and clinical observation have shown that negative words are traditionally used to warn patients of an impending painful stimuli. Though, in contrary to common beliefs and practices, this type of warning can increase their pain and anxiety. Using words with negative emotional content has even a greater aggravating impact than the positive impact of using words with positive emotional content. However, the studies that explored the impact of such messages have two limitations: they were not conducted in the ED context, and the effect attributable to caregivers themselves was little studied. Also, caregivers who deliver a message with positive or negative content in the context of a study are aware of this message and therefore are not blinded to the intervention arm. Thus, this absence of a double-blind study introduces the possibility of a bias, i.e. that the benefit of a positive message can be mediated by the caregivers and caregiver-patient interaction in a more global aspect and not simply by the verbal content of the message. It is indeed possible that caregivers, more or less consciously, may add additional elements in their communication that are congruent with the message studied, whether in the field of verbal or non-verbal communication (voice tone, warmth, empathy, etc.).

Objective(s):	The purpose of this study is to investigate whether the modulation of an information regarding a PIC insertion in the ED has an impact on patients' pain and anxiety levels. It also aims to determine if this effect is comparable, whether the message is delivered through a standardized audio recording or directly by caregivers. Finally, it aims to explore whether there are differences in patients' and caregivers' assessments of pain and anxiety.
Outcome(s):	<p>The primary outcomes, i.e. the intensity and unpleasantness (emotional component) of the pain experienced by patients during PIC insertion, will be measured using a Visual Analog Scale (VAS). Patients' anxiety state, as a secondary outcome, will also be measured by VAS. These three measurements will be performed after the PIC is inserted using three rulers presented to patients.</p> <p>Caregivers' assessment of patients' intensity and unpleasantness of pain and anxiety will also be measured using the three VAS, this time in paper format, and reported to the CRF after the PIC is placed. Patients and caregivers will be asked to rate their VAS without each other's knowledge.</p> <p>Before inserting the PIC, patients will assess the intensity and unpleasantness of any pre-existing pain and their basal anxiety level with these same three VAS. This will give a baseline value for these three measures. These values will be reported in the CRF before the PIC is placed, along with the reason for consultation (internal medicine, traumatology or surgery) and any painkillers already given/ongoing in the ED.</p> <p>Caregivers' behaviour will be assessed during the procedure according to the criteria described by Kaptchuck. The algic behaviour of patients during PIC insertion will also be evaluated using the Algoplus scale.</p> <p>The procedure's characteristics (location, caliber, number of attempts, difficulties and complications encountered), the demographic characteristics of the patients (sex, age, origin, level of education) and the demographic characteristics of the caregivers (sex, age) will be reported in the CRF after the PIC is placed. Patients will also be asked two questions (« Are you generally afraid of needles? », « Do you suffer from chronic pain, i.e. that has lasted for more than 3 months? ») to contextualize their VAS and chronic analgesic use will be reported.</p> <p>Finally, in the second phase, a unique coded number related to the study (study number) will be assigned to each caregiver and entered in the CRF when the PIC is placed. If needed, it will allow the analysis of data by clustering patients by caregiver.</p>
Study design:	Interventional, prospective, randomised, active control, double blind (patient, caregiver, Co-investigator) for the first phase, single blind (patient) for the second phase.

<p>Inclusion / Exclusion criteria:</p>	<p>The population of interest will include patients admitted to the LUH ED. Patients meeting all of the following inclusion criteria will be eligible to participate in this study:</p> <ul style="list-style-type: none"> • Patient ≥ 18 years old; • Patient whose management requires the placement of a first PIC; • Placement of the PIC on the upper limb. <p>Patients with any of the following exclusion criteria will be excluded from this study:</p> <ul style="list-style-type: none"> • Clinically unstable patient (passing through the resuscitation room or judged as such by the physician in charge of the case); • Patient incapable of decision-making capacity or with whom it is difficult to communicate: <ul style="list-style-type: none"> ○ Altered mental status (e.g. cognitive impairment, mental retardation, acute confusional state, acute psychosis); ○ Altered mental status due to recreational drug use; ○ Intoxication; ○ Patient unable to sufficiently communicate in French to give informed consent and answer questions about pain and anxiety; ○ Hearing impaired patient; • Patient unable to use the rulers (e.g. blind patient); • Altered upper limb (e.g. sensitivity disorders, lymphoedema); • Incarcerated patient; • Patient transferred from another hospital; • Patient who has already participated in this study during a previous visit; • Patient who knows the tested component (i.e. clinical communication) before the intervention; • Patient, caregiver or co-investigator who knows the content of the message assigned before the intervention (for the first phase of the study).
---	---

Measurements and procedures:	<p>Information delivered to patients about the placement of the PIC will be either a message that is usually delivered, or a message with positive content, avoiding negative words and suggesting specific notions of control and comfort related to the procedure. This intervention study will be carried out in two sequential phases, identical in every aspect except for the vector of messages (delivered by audio recordings in the first phase, directly by the caregivers themselves in the second phase). It will take place in the ED of the LUH between October 2017 and October 2019. All patients admitted to this department will be eligible for inclusion. Data collection will be possible every day of the week between 7am and 10pm. The co-investigators will divide the workload and only one of them will be present during each intervention. After consulting the patient's medical records in the ED and checking with the case's caregivers to ensure that there are no exclusion criteria, the co-investigators will introduce themselves to the patients and offer them to participate in the study. The co-investigators will explain to patients that, given the fact that their medical care involves the placement of a PIC, they are eligible for this study aimed at improving the care of patients visiting the ED during such a procedure. Should patients require additional information, the co-investigators will simply state that the study's primary objective is to assess the technical characteristics of the PIC placement. After verifying that all inclusion criteria and none of the exclusion criteria have been met, and that each participant has given his or her verbal consent, each participant will be randomized in a 1:1 ratio between the two arms of the study, in a double-blind design (patient, caregiver, co-investigator) in the first phase and single-blind (patient) in the second phase. The co-investigators will collect some additional standardized data according to the CRF. Then they will report to the caregivers that they can prepare patients for the PIC insertion (installation of the tourniquet, vein tracking and site disinfection). In the first phase, a test audio clip and a recorded introductory clip will be played to the patients before the caregivers prepare them for the procedure. Once these preparations are completed, the co-investigators will play the recorded audio intervention or control message to the patients in the first phase or the caregivers will deliver one of the two alternative messages directly before puncturing the patients in the second phase. In both cases, the co-investigators will complete the collection of data according to the CRF, first from patients and then from caregivers. Once all the data has been collected, a complete information sheet and consent form will be provided to patients, along with additional explanations when requested. Patients will have a minimum of 15 minutes to sign the consent form. Excluding this 15 minutes reflection period, participation in the study should not exceed 20 minutes and will be unique.</p>
Intervention:	<p>The intervention message delivers information with a positive content, avoiding negative words and suggesting specific notions of control and comfort related to the procedure. This message is delivered by an audio recording in the first phase of the study, then by caregivers in the second phase. The message duration should not exceed 1 minute.</p>
Control Intervention:	<p>The control message delivers information based on what is usually said to patients before a PIC is applied. This message is delivered by an audio recording in the first phase of the study, then by caregivers in the second phase. The message duration should not exceed 1 minute.</p>
Number of Participants with Rationale:	<p>See the « Statistical considerations » section of the Study synopsis.</p>
Study Duration:	<p>2 years</p>
Study Schedule:	<p>October, 1st. 2017 October, 1st. 2019</p>

Co-investigator(s):	<p>Co-investigator: Anne Beyeler, 1st year M.A. Medical Student, UNIL, Lausanne, Switzerland</p> <p>Co-investigator: Adélaïde Le Bloc'h, 1st year M.A. Medical Student, UNIL, Lausanne, Switzerland</p> <p>Co-investigator: Hélène Gerhard-Donnet, research nurse, Emergency Department, LUH, Lausanne, Switzerland</p>
Study Centre(s):	Monocentric study, Emergency Department of the LUH
Statistical Considerations:	<p>Analyses will be performed using Stata software version 14 (StataCorp, TX, USA). Descriptive data will be presented by mean and standard deviation, median and interquartile space or proportions for Gaussian, non-Gaussian, and categorical variables, respectively. The comparison between randomized groups will be done by Student t-test or Wilcoxon rank sum test for continuous variables, and by Chi2 or Fisher exact test for categorical variables, as appropriate.</p> <p>This study aims to demonstrate the superiority of an information message with a positive content on the pain intensity when a PIC is inserted. The mean intensity of pain is estimated at 34 mm using a VAS (with a possible intensity between 0 and 100 mm), with a standard deviation estimated at 24 mm when a PIC is placed. To detect the smallest decrease in clinically significant pain intensity of 13 mm caused by the procedure, a sample of 110 patients, or 55 patients per arm, is required, setting the power at 80%, with an alpha threshold of 0.05. Taking into account missing values or refusal to participate after randomization estimated at 10% of patients, 60 patients will be randomized per arm. A total of at least 240 patients will therefore be recruited for the two phases, i.e. the four arms, of the study.</p>
GCP Statement:	The study will be carried out in accordance to the protocol and with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by ICH, the Swiss Law and Swiss regulatory authority's requirements.

ABBREVIATIONS

CA	Competent Authority (e.g. Swissmedic)
CEC	Competent Ethics Committee
ClinO	Ordinance on Clinical Trials in Human Research
CRF	Case Report Form
ER	Emergency room
FOPH	Federal Office of Public Health
GCP	Good Clinical Practice
HFG	Humanforschungsgesetz (Law on human research)
HMG	Heilmittelgesetz (Law on medicines)
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICTRP	International Clinical Trials Registry Platform
ISO	International Organisation for Standardisation
IUMSP	Institut Universitaire de Médecine Sociale et Préventive (University Institute of Social and Preventive Medicine)
Kofam	Koordinationsstelle Forschung am Menschen (Coordination Office Research on Human Beings)
LPTH	Loi sur les produits thérapeutiques (Therapeutic Products Act)
LRH	Loi fédérale relative à la recherche sur l'être humain (Federal Law on Human Research)
LUH	Lausanne University Hospital
OMS	Organisation mondiale de la Santé (World Health Organisation, WHO)
PI	Principal Investigator
PIC	Peripheral Intravenous Catheter
SNCTP	Swiss National Clinical Trials Portal
VAS	Visual Analog Scale

STUDY SCHEDULE

This prospective, randomized, controlled and monocentric intervention study will be conducted in two sequential phases, identical in every aspect except for the message vector. The first phase will consist of delivering one of two alternative messages to all patients using a standardized audio recording. Once the required sample size has been reached for the first phase, the second phase will begin. In this phase, one of the two alternative messages will be delivered by the caregivers themselves. Patient participation will be unique and should not exceed 20 minutes.

<i>First phase of the study</i>	<i>Screening</i>	<i>Intervention - message delivered by an audio recording</i>	<i>Debriefing</i>
<i>Time (minutes)</i>	-10	0	10
<i>Inclusion and exclusion criteria</i>	-2		
<i>Patient partial information and verbal consent</i>	-4		
<i>Randomisation</i>	-1		
<i>Patient listen to the audio recording</i>		1	
<i>Measurement and report of variables in the CRF</i>	-2	x	2
<i>Adverse events</i>		x	x
<i>Patient's complete information and written consent (a posteriori)</i>			8

<i>Second phase of the study</i>	<i>Screening</i>	<i>Intervention - message delivered by the caregiver</i>	<i>Debriefing</i>
<i>Time (minutes)</i>	-10	0	10
<i>Inclusion and exclusion criteria</i>	-2		
<i>Patient partial information and verbal consent</i>	-4		
<i>Randomisation</i>	-1		
<i>Communication of the caregiver</i>		1	
<i>Measurement and report of variables in the CRF</i>	-2	x	2
<i>Adverse events</i>		x	x
<i>Patient's complete information and written consent (a posteriori)</i>			8

1. STUDY ADMINISTRATIVE STRUCTURE

1.1 Sponsor, Principal Investigator

Principal Investigator, Sponsor: Dr O. Hugli, MD, MPH, Emergency Department, BH 09-777, LUH, Rue du Bugnon 46, 1011 Lausanne, Switzerland. Tél : 021 314 05 67. Email : Olivier.Hugli@chuv.ch.

Sponsor : Lausanne University Hospital (LUH), Rue du Bugnon 46, 1011 Lausanne, Switzerland.

1.2 Co-investigators

Co-investigator, Co-sponsor: Dre C. Berna, MD-PhD, Antalgia Center, Anesthesiology Department, BH 06, LUH, Rue du Bugnon 46, 1011 Lausanne, CH. Tél: 021 314 20 40. Email: Chantal.Berna-Renella@chuv.ch.

Co-investigator: Anne Beyeler, 1st year M.A. Medical Student, UNIL, Lausanne, Switzerland. Tél: 079 758 89 69. Email: Anne.Beyeler@unil.ch.

Co-investigator: Adélaïde Le Bloc'h, 1st year M.A. Medical Student, UNIL, Lausanne, Switzerland. Tél: 077 483 57 18. Email: Adelaide.Lebloch@unil.ch.

Co-investigator: Hélène Gerhard-Donnet, research nurse, Emergency Department, BH05, LUH, Rue du Bugnon 46, 1011 Lausanne, Switzerland. Tél: 079 556 38 99.

1.3 Statistician ("Biostatistician")

The principal investigator, with the support of the IUMSP methodological and biostatistical consultation.

1.4 Laboratory

Non-applicable.

1.5 Monitoring institution

Marie-France Derkenne, research nurse, Emergency Department, BH05, LUH, Rue du Bugnon 46, 1011 Lausanne, Switzerland. Tél: 079 556 38 99.

1.6 Data Safety Monitoring Committee

Non-applicable.

1.7 Any other relevant Committee, Person, Organisation, Institution

Non-applicable.

2. ETHICAL AND REGULATORY ASPECTS

The decision of the CEC concerning the conduct of the study will be made in writing to the principal investigator before the beginning of this study. The clinical study can only begin once approval from all required authorities has been received. Any additional requirements imposed by the authorities shall be implemented.

2.1 Study registration

Registration on the FOPH's SNCTP and clinicaltrials.gov once the study has been approved by the CEC.

2.2 Categorisation of study

This prospective, randomized, controlled and monocentric intervention study belongs to the category of other clinical trials in the sense of ClinO Art. 60. Since its purpose is to assess the impact of specific information on patients' pain and anxiety when placing a PIC in the ED, it does not consist of a clinical trial of standardized therapeutic products or transplants, nor does it consist of a transplant clinical trial.

It compares the impact of an information message usually delivered when a PIC is applied to a message with positive content. This intervention concerns only a very brief information, relating to a procedural gesture required when dealing with emergencies and aims to deliver a positive message. It therefore involves minimal risks. The constraints are also minimal since the participation of patients, in parallel with a gesture necessary for their clinical management, will be unique and limited in time. It is therefore a risk category A study in the sense of ClinO Art. 61.

2.3 Competent Ethics Committee (CEC)

Investigators ensure that approval by an appropriate CEC has been obtained for this study. They will report to the CEC any serious adverse event within 7 days. They will also inform the CEC within 15 days in case of early termination or discontinuation of the study. The planned completion of the study will be report to the CEC within 90 days. A final report will be submitted within one year of the completion of the data collection, in the form of a Master's degree work.

No substantial amendments to the protocol shall be made without the prior approval of the CEC, except in cases where such changes would be necessary to address an immediate and apparent risk to study participants.

2.4 Competent Authorities (CA)

Non-applicable.

2.5 Ethical Conduct of the Study

The study will be carried out in accordance to the protocol and with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by ICH, the Swiss Law and Swiss regulatory authority's requirements. The CEC and regulatory authorities will receive an annual safety report and will be informed about study start/end in agreement with local requirements.

2.6 Declaration of interest

Investigators state that they have no conflict of interest in relation to this study.

2.7 Patient Information and Informed Consent

Co-investigators will explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may cause. Participants will be informed that the participation in the study is voluntary and that they may withdraw from the study at any time without affecting their care. They will also be informed that their participation in the study will not be remunerated.

Participants will be informed that their medical files may be examined by authorised individuals other than their treating physician.

Participants will be briefly informed by the co-investigators at the beginning of the study. Indeed, mentioning that the study aims to investigate the effects of communication on pain and anxiety and

that two messages with different content will be tested could create expectations and skew the results of the study. Thus, the co-investigators will only collect their verbal consent at this stage. The content of this partial verbal information will be based on the partial information template (Appendix 1).

A complete information sheet describing the study and the information needed for participants to make an informed decision about their participation will be provided once the data have been collected, along with a consent form (Appendices 2 and 3). Participants will have at least 15 minutes to make a final decision on whether or not to participate in the study and, if so, sign the consent form. In the event that participants refuse to sign it, their data will be physically destroyed using a shredder, except for data relating to their sex and age. These data will be kept for statistical purposes in a separate document (Appendix 7). The consent form will also be signed and dated by one of the co-investigators and will be an integral part of the study documents. Participants will be provided with a copy of the signed consent form.

2.8 Participant privacy and confidentiality

Investigators affirm and uphold the principle of the participant's right to privacy and that they shall comply with applicable privacy laws. Especially, anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Subject confidentiality will be further ensured by utilising subject identification code numbers to correspond to treatment data in the computer files.

For data verification purposes, authorised representatives of the principal investigator or of the CEC may require direct access to parts of the medical records relevant to the study, including participant's medical history.

2.9 Early termination of the study

The principal investigator may terminate the study prematurely according to certain circumstances, for example:

- ethical concerns;
- insufficient participant recruitment;
- when the safety of the participants is doubtful or at risk, respectively;
- alterations in accepted clinical practice that make the continuation of a clinical trial unwise.

2.10 Protocol amendments

Investigators are authorized to amend the protocol. However, any substantial amendment must be communicated in writing to the CEC and clinical trial registries. It must also be mentioned in any subsequent publication.

Substantial amendments will only be implemented after approval of the CEC. However, under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the CEC. Such deviations shall be documented and reported to the CEC as soon as possible.

All non-substantial amendments to the protocol will be reported to the CEC in the annual safety report.

3. BACKGROUND AND RATIONALE

3.1 Background and Rationale

The occurrence of a medical and surgical emergency is a stressful life event. An ED is also a noisy and sometimes chaotic environment, contributing in itself to increase the anxiety associated with the reason for consultation. Some common medical procedures, such as a peripheral intravenous catheter (PIC), can, in addition to inducing pain, exacerbate this anxiety or a pre-existing pain. However, the well-being of patients, especially during invasive medical procedures, can be improved by various communication techniques (Lang et al., 2000). However, the literature and clinical observation suggest that negative words have traditionally been used to warn patients of an impending painful stimulus (Varelmann et al., 2010; Dutt-Gupta et al., 2007; Lang et al., 2005). In line with these publications, the following sentences were noted during an observation day at the LUH ED: « It might hurt a little. », « I'm gonna hurt you a little bit. », « I'm going to puncture you, don't move. », « I puncture. », « Don't move. », « Let me do it. ». Though, contrary to common beliefs and practices, this type of warning can increase patients' pain and anxiety (Varelmann et al., 2010; Lang et al., 2005). Using words with negative emotional content has even a greater aggravating impact than the positive impact of using words with positive emotional content (Greville-Harris et al., 2015; Wang et al., 2008). However, the studies that explored the impact of such messages have two limitations: they were not conducted in the context of emergencies, and the effect attributable to caregivers themselves was little studied. Also, caregivers who deliver a message with positive or negative content in the context of a study need to be aware of this message and therefore of the arm of the intervention. This absence of a double-blind study introduces the possibility of a bias, i.e. that the benefit of a positive message can be linked to caregivers and caregiver-patient interaction in a more global way and not simply to the verbal content of the message. It is indeed possible that caregivers, more or less consciously, may add additional elements in their communication that are congruent with the message studied, whether in the field of verbal or non-verbal communication (voice tone, warmth, empathy, etc.).

3.2 Investigational Product (treatment, device) and Indication

The teaching of physician-patient communication as proposed by the Swiss Academy of Medical Sciences postulates that « *the transmission of information is intended to inform the patient in such a way that he/she is able to correctly assess the diagnosis, the type of intervention, its course, its purpose, its usefulness and the risks associated with it* » (ASSM, 2013). No details are given on how to deliver information about a painful procedure, let alone on how to limit its painful and anxious impact. The issues surrounding patients' informed consent (Wells et al., 2012) and the elements to be disclosed during the conduct of a procedure are debated and researched, the issue being that it is essential to use precise and detailed vocabulary in order to obtain informed consent. Nevertheless, more positive or less explicit words could be used in the procedure itself (Lang et al., 2005). In addition, caregivers often confuse the consent phase (before initiating the procedure) and the description phase of the procedure while it is in progress (« procedural disclosure » - procedural information) which is not mandatory and not necessarily helpful (Krauss, 2015). Lang proposes to separate these two phases temporally. Thus, the elements necessary to be able to base informed consent (technical characteristics, adverse reactions, etc.) should be detailed before the procedure, whereas during the procedure only open-ended questions (« What do you feel? »), neutral statements or positive suggestions should be used (Lang et al., 2005). This study focuses only on procedural information relating to the placement of the PIC, the co-investigators intervening only after the information on which informed consent is based has been provided. The purpose of the intervention is then to modulate this specific procedural information given to patients when a PIC is placed in the Emergency Department.

The primary objective of this study is thus to compare the effect on painful feelings induced by the insertion of a PIC in the ED: 1) by two different ways of communicating information; 2) by two different vectors of the message. To achieve the first objective, the study will compare the effect of a usual message to prepare patients for the painful stimulus during PIC insertion with the effect generated by a message with positive content. The latter will not contain explicit words such as « pain, sting, needle », but instead words suggesting specific notions of control and comfort related to the procedure. The main objective of this study is thus to determine whether the use of positive language during the insertion of a PIC in the ED improves patients' pain experience compared to usual language practices. As for the second objective, the effect of the message vector, it will be studied by testing if the effect of this positive language is comparable, whether the message is delivered by a standardized audio recording or directly by the caregiver performing the procedure.

Secondarily, this study aims to explore the effect of the intervention on patients' anxiety. Finally, it

seeks to explore the differences that may exist between an assessment of pain and anxiety made by patients (feelings of pain and anxiety) and that made by caregivers (estimated pain and anxiety) as well as the possible determinants of these differences, if they exist (patients: sex, age, origin, level of education / caregivers: sex, age).

3.3 Preclinical Evidence

Non-applicable.

3.4 Clinical Evidence to Date

A systematic review, including a meta-analysis of 51 studies (5,079 patients) was conducted in 2015 about the effect of patient-caregiver communication on pain (Mistiaen et al., 2016). Because interventions on communication can be very diverse, this review classified the interventions of the different studies into three categories: cognitive, emotional and procedural interventions. In the sense of this systematic review, our intervention is part of cognitive interventions, seeking to elicit negative/neutral/positive expectations in patients, and of procedural interventions, seeking to prepare patients for an invasive procedure. Particularly in procedural interventions, our intervention consists in the transmission of procedural information (description of events: what, when and how) and sensory (description of the sensory aspects of the procedure) as well as behavioural instruction (explain to patients what they should do in order to facilitate the procedure). With respect to cognitive interventions, 13 of the 19 studies included in the review found significant differences between groups with a general tendency to reduce pain for groups with positive or neutral suggestion versus those with negative suggestion or control. Of the 6 randomized controlled studies that had applied cognitive interventions to acute pain and measured pain intensity, 2 studies reported that positive suggestions reduced pain and 2 studies reported that negative suggestions increased pain, with the last 2 studies finding no effect on both. According to this systematic review, negative suggestions would thus increase the painful feelings while positive suggestions would reduce them, but the extent of the effect is not clear and the overall quality of the studies was low. Concerning the transmission of procedural and sensory information, alone or in combination with other procedural interventions such as behavioural instruction, they tend to lead to a reduction in pain, although the amount of information required is uncertain and a possible excess of information is harmful. Finally, the systematic review concludes that educating patients in an empathetic and positive way reduces their painful symptomatology. However, we note that none of the studies included in the systematic review were carried out in Switzerland, which may have its own peculiarities in terms of pain feelings, expression and evaluation of pain.

3.5 Dose Rationale / Medical Device: Rationale for the intended purpose in study (pre-market MD)

Non-applicable.

3.6 Explanation for choice of comparator (or placebo)

In this study, we chose to compare a message content commonly used in invasive medical procedures with a message content that is positive. While it may be useful to create a « no communication » group to position the two messages in relation to each other, total silence on the part of caregivers when placing the PIC may be poorly perceived by patients and caregivers. This would be an intervention well beyond the usual practice and difficult to ask from caregivers.

The control message was developed based on the literature (Varelmann et al., 2010; Dutt-Gupta et al., 2007; Lang et al., 2005; etc.) and clinical practices identified during an observation day in the LUH ED conducted to assess the practicality of this study. The content of these messages is detailed in section 8 « Study intervention ».

3.7 Risks / Benefits

No specific risk is expected for this very brief intervention, only modulating a procedural information. Should any adverse event occur as a result of the intervention, it will be spontaneously reported in the CRF by the co-investigators during the intervention and, if necessary, forwarded to the CEC. Investigators are available to participants during and after the study (as it is mentioned in the full information sheet).

An observation day at the LUH ED was conducted in order to assess the practical feasibility of this study and to minimize disruption to the caregivers' work. This will allow most of the data to be

collected before and after the insertion of the PIC, without interfering with caregivers' work.

In addition, the listening device will be systematically disinfected by co-investigators after use. By default, an earphone device will be made available to patients. In the event of refusal, unsuitable morphology or wearing a hearing aid, a headphone device may be provided.

If this study is able to demonstrate that positive communication during a PIC insertion effectively reduces patients' pain and anxiety, it will be a simple teachable intervention that can be easily transposed into current clinical practice and could improve management of the PIC insertion, a very common practice in EDs. If this message can also be delivered by audio recording, with good effects, such communication could be considered for procedures known to be painful or anxious. Indeed, if the study demonstrates a reduction in pain and anxiety, it would indicate a new approach to multimodal pain management in EDs. These results would therefore not only have the potential to change the practice of caregivers during painful procedures in emergencies, but also to encourage the integration of these notions of communication in their training. This study would also contribute to a better understanding of the placebo and nocebo effects of communication and help improve caregiver-patient communication.

3.8 Justification of choice of study population

The population targeted by this study includes medically stable patients in the ED whose management requires the insertion of a CIP. This medical procedure is performed daily in the ED without prior analgesia. Initiating a reflection on how to reduce its painful and anxious impact is therefore relevant and necessary. It is also easier to carry out this type of study in the ED because the necessary number of patients is guaranteed.

Patients who are clinically unstable, incapable of decision-making or with whom it is difficult to communicate are excluded. Thus, this study does not target a vulnerable population, although these are emergency situations. Moreover, patients will be able to reconsider their decision to participate in the study at any time and will be given a minimum of 15 minutes to complete the data collection process before signing the consent form. Since the medical management of patients is independent of the study, the emergency physician responsible for the patient may also decide to withdraw him/her from the study in order to safeguard his/her interests and provide appropriate management.

4. STUDY OBJECTIVES

4.1 Overall Objective

The overall objective of this study is to investigate if the modulation of the information when inserting a PIC in the ED has an impact on patients' pain and anxiety levels and if this effect is comparable, whether the message is delivered through a standardized audio recording or directly by caregivers. It also explores if there are differences in patients' and caregivers' assessments of pain and anxiety.

4.2 Primary Objective

The primary objective of this study is to determine if the use of a positive information, avoiding negative words and suggesting specific notions of control and comfort related to the procedure, when inserting a PIC in the ED, reduces pain intensity when compared to the usual language practices.

The primary objective is also to determine if this effect is comparable, whether the message is delivered by a standardized audio recording or by the caregiver performing the procedure.

4.3 Secondary Objectives

Secondarily, this study aims to explore the effect of the intervention on patients' anxiety.

Finally, it seeks to explore the differences that may exist between an assessment of pain and anxiety made by patients (feelings of pain and anxiety) and that made by caregivers (estimated pain and anxiety) as well as the possible determinants of these differences, if they exist (patients: sex, age, origin, level of education / caregivers: sex, age).

4.4 Safety Objectives

Non-applicable.

5. STUDY OUTCOMES

5.1 Primary Outcomes

The primary outcome of this study will be patients' assessment of the intensity and unpleasantness (emotional component) of their pain during the insertion of the PIC.

5.2 Secondary Outcomes

The secondary outcomes of this study will be patients' assessment of their anxiety at PIC insertion and caregivers' assessment of patients' pain intensity and unpleasantness and anxiety at PIC insertion (Singer et al., 1999).

Other co-variables will be reported in the CRF to the extent that they may influence primary or secondary outcomes:

- The intensity and unpleasantness of pain and anxiety level assessed by patients prior to the CIP;
- Reason for consultation (internal medicine, traumatology or surgery);
- Any painkillers already given/ongoing in the ED (what, when, administered by whom);
- The caregivers' behaviour during the procedure;
- The patients' algic behaviour during the procedure;
- Procedure' characteristics (location, caliber, number of attempts, difficulties and complications encountered);
- Report of a possible fear of needles (« Are you generally afraid of needles? »);
- Report of a possible chronic pain (« Do you suffer from chronic pain, i.e. that has lasted for more than three months? ») and chronic painkillers consumption.

The sex, age, origin and educational background of patients, as well as the sex and age of caregivers, will also be reported to the extent that they may influence caregivers' assessment of patients' pain intensity and unpleasantness and anxiety level (Li et al., 2001; Nevin, 1996; Singer et al., 1999).

Finally, in the second phase, a unique coded number related to the study (study number) will be assigned to each caregiver and reported in the CRF when the PIC is inserted. If needed, it will allow the analysis of data by grouping patients by caregiver.

5.3 Safety Outcomes

Non-applicable.

6. STUDY DESIGN

6.1 General study design and justification of design

It is an interventional, prospective, randomized, active-controlled, monocentric intervention study. It will take place in the LUH ED between October 2017 and October 2019. All patients admitted to this service will be eligible for inclusion. Data collection will be possible every day of the week between 7am and 10 pm in order to obtain a sample that is as representative as possible of an ED's population. In order to be able to cover as many hours as possible, the co-investigators will divide them among themselves and, at each intervention, only one of them will be present. Dr O. Hugli and Dre C. Berna will not participate in data collection.

After consulting the patient's medical records in the ED and checking with the patient's caregivers that there are no exclusion criteria, the co-investigators will introduce themselves to the patients and invite them to participate in the study. The co-investigators will explain to the patients that, given the fact that their medical care involves the insertion of a PIC, they are eligible for this study aimed at improving the care of patients visiting the LUH ED during such an act. Should patients require additional information, the co-investigators will simply state that the study's primary objective is to assess the technical characteristics of the PIC insertion. At this stage, only a verbal agreement will be required. After verifying that all inclusion criteria have been met, that none of the exclusion criteria are applicable and obtaining a verbal consent, patients will be randomized in a 1:1 ratio between the two arms of the study, in a double-blind design (patient, caregiver, co-investigator) in the first phase and in a single-blind design (patient) in the second phase. The co-investigators will collect some additional data in a standardized manner by following the CRF and then report to the caregivers that they can prepare the patients for PIC insertion (installation of the tourniquet, vein tracking and site disinfection). In the first phase, a test audio clip and a recorded introductory audio clip will be played to the patients before the caregivers prepare them for the procedure. Once these preparations are completed, the co-investigators will play the recorded audio intervention or control message to the patients in the first phase or the caregivers will deliver one of the two alternative messages directly before puncturing the patients' vein in the second phase. In both cases, the co-investigators will complete the collection of data according to the CRF, first from patients and then from caregivers. Once all the data has been collected, a complete information sheet and consent form will be provided to the patients, along with additional explanations when requested. Patients will have a minimum of 15 minutes to sign the consent form. Excluding this 15 minutes reflection period, participation in the study should not exceed 20 minutes and will be unique.

The study is divided into two phases for organizational reasons. Indeed, it implies a perfect understanding and cooperation of the caregivers who perform the PIC insertion, their verbal and non-verbal behaviour should not interfere with the progress of the study. Thus, planning two successive arms, with an appropriate information session in each phase, instead of four arms conducted simultaneously at the same time, will limit unnecessary confusion and loss of included patients.

The variables will be reported in a standardized manner in the CRF in the following order:

- Before the insertion of the PIC:
 - Patient's identification number;
 - Inclusion and exclusion criteria;
 - Reason for consultation;
 - Antalgia already given/ongoing in the ER;
 - Patient's VAS relative to pain intensity, discomfort and anxiety.
- Around the insertion of the PIC:
 - Caregiver's behaviour.
- During the insertion of the PIC:
 - Message delivered;
 - Patient's behaviour.
- After the insertion of the PIC:
 - Procedure's characteristics (location of the PIC, PIC caliber, number of attempts before successful installing the PIC, difficulties and complications encountered);
 - Patient's VAS relative to pain intensity, discomfort and anxiety;
 - Report of a possible fear of needles (« Are you generally afraid of needles? »);
 - Report of a possible chronic pain (« Do you suffer from chronic pain, i.e. that has lasted for more than three months? ») and chronic painkillers consumption;

- Patient's demographics;
- Occurrence of potential inconveniences;
- Obtaining written consent;
- Caregiver's study number (only for the second phase);
- Caregiver's VAS relative to patient's pain intensity, discomfort and anxiety level;
- Caregiver's demographic characteristics.

6.2 Methods of minimising bias

6.2.1 Randomisation

In the first phase of the double-blind study, a randomization method by permutation of blocks of 4 and 6 patients will be used. The principal investigator, who will not collect data, will create the randomization list and hold the randomization seed.

In the second phase, only patients will be blind, but the assignment of one of the two messages will also be done by block permutation of 4 and 6.

In both phases of the study, randomization will occur immediately after verbal consent, before the intervention or control message is delivered.

6.2.2 Blinding procedures

During the first phase, the allocation of the arm « control message » or of the arm « intervention message » will be determined by a code written on a card inside a sealed and opaque envelope, prepared by the principal investigator. This code will indicate the number, between 1 and 130, of the audio track to be played to the patient and will be recorded in the CRF. In the second phase, the note « control message » or « intervention message » written on the card will indicate to the caregivers the message to be delivered and will be reported in the CRF. Envelopes will be numbered consecutively, and the co-investigators will open them consecutively, noting each time the opening date. The principal investigator will regularly verify that the order of opening is respected by checking the number of envelopes opened and the opening dates against the number of patients included in the study.

The first phase of the study will be carried out in double blind (patient, caregiver, co-investigator) thanks to the coding of audio recordings. In the second phase, only patients will be blinded to the tested component.

6.2.3 Other methods of minimising bias

Based in particular on the limitations identified from the studies included in the 2015 systematic review (Mistiaen et al., 2016), the following measures were taken to minimize as much as possible the bias that could result from this study:

- Integrity of the intervention: most of the studies included in the systematic review had not verified the accuracy of their intervention. In both phases of our study, caregiver behaviour will be reported in the CRF according to Kaptchuck criteria. In the first phase of the study, caregivers will be instructed to act naturally with patients during the procedure, without referring to the ongoing study throughout the entire duration of the procedure or commenting early on the PIC placement. Any interactions will be reported in the CRF under the « Difficulty(-ies) encountered » category. In the second phase, the script as it has been verbalized by the caregivers will also be globally reported. The content of the message delivered by caregivers will be reported in writing to the CRF as key words/concepts, checked off once they have been stated. For key words/concepts that would not be included in the original script, but which would still be mentioned by caregivers, they will be reported specifically under the « Other(s) » category. We have also scheduled for each phase an information session for the emergency care staff on the progress of the study and the content of the messages at one of their monthly team meeting, which will then be the subject of a report sent to the entire team;
- Statistical considerations: most of the studies included in the systematic review had not calculated an *a priori* statistical power, and since many studies included a small number of patients (from 19 to 771 with an average of 110 patients per study), divided into several intervention arms, the probability was high that a real effect could not be detected. We calculated an *a priori* statistical power in our study and set a minimum number of participants at 240;
- Retention of baseline demographic data (sex, age) of patients who have revoked consent or who were excluded from the study to ensure that they are similar to patients included on these

two criteria;

- Intervention control not described: we plan to transcribe the texts of the messages intervention and control in the presentation of the results of the study;
- Lack of blindness: the risk of bias was considered significant in most of the studies included in the systematic review due to the lack of blindness of practitioners, patients and observers. However, our study will be done in double blind during the first phase, then simple blind for the second. Furthermore, in both phases, patients will initially not be informed of the fact that the study's purpose is communication, let alone that two alternative messages will be tested, which limits bias in their evaluations;
- Use of validated tools wherever possible;
- Reporting of patient behaviour during the PIC insertion;
- Playing of a test audio clip, preceding the audio messages recorded and common to all participants, so that the sound level can be adjusted appropriately;
- Pilot phase « Messages » - Reactions to the listening of recorded audio messages;
- Pilot phase « Rating » - Evaluation of the ability of the co-investigators to rate the same way identical behaviour.

6.3 Unblinding Procedures (Code break)

Only the principal investigator will hold the coding key and it will only be revealed once all the data has been collected, entered into the database and statistically analyzed.

In case of an urgent situation, the allocation to one of the arms can be obtained from the principal investigator.

7. STUDY POPULATION

7.1 Eligibility criteria

Patients meeting all of the following inclusion criteria will be eligible to participate in this study:

- Patient ≥ 18 years old;
- Patient whose management requires the placement of a first PIC;
- Placement of the PIC on the upper limb.

Patients with any of the following criteria will be excluded from the study:

- Clinically unstable patient (passing through the resuscitation room or judged as such by the physician in charge of the case);
- Patient without decision-making capacity or with whom it is difficult to communicate:
 - Altered mental status (e.g. cognitive impairment, mental retardation, acute confusion state, acute psychosis);
 - Altered mental status due to recreational drug use;
 - Intoxication;
 - Patient unable to sufficiently communicate in French to give informed consent and answer questions about pain and anxiety;
 - Hearing impaired patient;
- Patient unable to use the rulers (e.g. blind patient);
- Altered upper limb (e.g. sensitivity disorders, lymphoedema);
- Incarcerated patient;
- Patient transferred from another hospital;
- Patient who has already participated in this study during a previous consultation;
- Patient who knows the tested component (i.e. clinical communication) before the intervention;
- Patient, caregiver or co-investigator who knows the content of the message assigned before the intervention (for the first phase of the study).

7.2 Recruitment and screening

All patients admitted to the LUH ED between October 2017 and October 2019 will be eligible for inclusion. A first evaluation of the inclusion and exclusion criteria by the co-investigators will be based on the patient's medical file in the ED and a discussion with the caregivers in charge of the case. These criteria will be re-evaluated by the co-investigators at the patients' bedside.

Participation in this study will not be remunerated.

7.3 Assignment to study groups

After verifying that all inclusion criteria have been met, that none of the exclusion criteria are applicable and that each participant has given his or her verbal consent, each participant will be randomized in a 1:1 ratio between the two arms of the study using the opaque and sealed envelopes mentioned in section 6.2.2 « Blinding procedures ».

7.4 Criteria for withdrawal / discontinuation of participants

Patients will be excluded from the study if they are aware of the tested component or of the messages' content prior to the intervention. They will also be excluded if they meet one of the exclusion criteria (e.g. instability, loss of decision-making capacity) before they can sign the consent form.

Patients will also be excluded from the study if caregivers or co-investigators have been made aware of their message prior to the intervention.

Differences in the script, patient or caregiver interventions will be reported in the CRF under the « Difficulty(-ies) encountered » category for inclusion in the data analysis but will not be grounds for exclusion from the study. The same will be true in the second phase for variations in the messages delivered by caregivers. They will be reported in the CRF under the « Verbal script » category but will not constitute grounds for exclusion from the study.

Patients may choose to revoke their consent at any time. If they do so, they will be removed from the study.

Data collected from patients who are excluded or who have revoked their consent will be physically

destroyed using a shredder, with the exception of data relating to their sex and age, which will be reported for statistical purposes (Appendices 8 and 7). Patients will receive a complete information sheet so that they can contact the investigators if they wish to do so.

Excluded patients or patients who have revoked their consent will be included in the calculation of the number of participants required to complete the collection of study data, but a 10% mark-up of this number is expected to compensate for these missing data.

8. STUDY INTERVENTION

8.1 Identity of Investigational Products

Regarding the first phase of the study:

- In order to adjust the sound volume properly, a test audio clip will be played to the patients. It will have the following content: « Hello. Thank you for your participation in this study. This is a sound volume test. Please tell the staff if you can hear me well, or if there's a problem. »
- An introductory sequence, identical for both groups, will also be played to the participants before the caregivers prepare them for the procedure (placement of the tourniquet, identification of the vein and site disinfection). It will have the following content: « This is a standard message regarding the following procedure, thank you for listening. As part of your medical care, the placement of a venous catheter is necessary. The caregiver will prepare your arm for the procedure. »
- The intervention and control messages will be played to patients once the caregivers have completed their preparations and are ready to sting the patients.

8.1.1 Experimental Intervention

First phase - Text of the recorded intervention message:

In the « intervention message » arm, the recorded message will be:

« It is possible that this arm may begin to feel a certain numbness, a kind of heaviness, or warmth, as if it was asleep during the procedure. Now that you've heard this message, you can signal the caregiver as soon as you're ready by lifting a finger from your other hand. »

The key elements are: dissociation of the arm, being ready, sense of control, anesthetic suggestion limited to the duration of the procedure.

Second phase - Text of the intervention message delivered by caregivers:

In order for the intervention to be credible, it is important that caregivers take ownership of the message to be delivered. Caregivers will then receive the original text, along with the key elements it contains and the contradictory elements to be omitted. They will be encouraged to formulate a variant that fits them but contains these key elements. A reminder of key elements will be provided at each clinical interaction. Some deviations from the script will be tolerated as long as the essential content of the message to be delivered is preserved and no contradictory elements are inserted. The content of the messages delivered by caregivers will be reported in writing in the CRF by the co-investigator in the form of key words/concepts, checked off once they have been stated. For key words/concepts that would not be included in the original script, but which would still be mentioned by caregivers, they will be reported specifically under the « Other(s) » category.

8.1.2 Control Intervention

First phase - Text of the recorded control message:

In the « control message » arm, the recorded message will be:

« You may feel the tourniquet on your arm, it's tight, maybe it's tingling. Stinging can hurt when the needle goes in, but don't move during the procedure. When this message stops, lift a finger from your other hand and the caregiver will sting you. »

The key elements are: contact with the tourniquet and its sensory aspect, then sensory aspects of the needle, lack of control.

Second phase - Text of the control message delivered by caregivers:

Similar to the text of the intervention message delivered by the caregivers in section 8.1.1 « Experimental intervention ».

8.1.3 Packaging, Labelling and Supply (re-supply)

Non-applicable.

8.1.4 Storage Conditions

Non-applicable.

8.2 Administration of experimental and control interventions

The intervention and control messages will be delivered by a standardised audio recording in the first phase of the study and then directly by the caregivers themselves in the second phase.

In the first phase of the study, caregivers will prepare patients for the PIC insertion according to the usual procedure (placement of tourniquet, vein tracking and site disinfection). As soon as these preparations are completed, the co-investigators will play the audio message recorded intervention or control to the patients. The end of the audio message will instruct patients to lift a finger from their other hand and, at that point, the caregivers will sting them and complete their procedure.

In the second phase, the message will be delivered by the caregivers themselves just before they sting the patients.

8.3 Dose / Device modifications

Non-applicable.

8.4 Compliance with study intervention

In order to ensure that the recorded messages are not perceived as artificial by patients, the audio recordings were tested and adapted until they were perceived as adequate in a « Messages » pilot phase.

Emergency care staff will be informed of the progress of the study and the content of the messages during one of their monthly team meeting, which will then be the subject of a report sent to the entire team. They will be asked to act naturally with patients during the procedure, without referring to the current study for the duration of the procedure, nor commenting early on the PIC placement. When the second phase of the study begins, emergency care staff will be more accurately informed and trained by co-investigators on how to deliver the messages.

Differences in the script, patient or caregiver interventions will be reported in the CRF under the « Difficulty(-ies) encountered » category for inclusion in the data analysis but will not be grounds for exclusion from the study. The same will be true in the second phase for variations in the messages delivered by caregivers. They will be reported in the CRF under the « Verbal script » category but will not constitute grounds for exclusion from the study.

8.5 Data Collection and Follow-up for withdrawn participants

In cases where patients ultimately refuse to sign the consent form or are excluded from the study, data collected in the study will be physically destroyed by a shredder, with the exception of data related to sex and age that will be reported for statistical purposes (Appendices 7 and 8). Patients will be given a copy of the complete information sheet so that they can contact the principal investigator if they wish to do so.

8.6 Trial specific preventive measures

Non-applicable.

8.7 Concomitant Interventions (treatments)

Non-applicable.

8.8 Study Drug / Medical Device Accountability

Non-applicable.

8.9 Return or Destruction of Study Drug / Medical Device

Non-applicable.

9. STUDY ASSESSMENTS

9.1 Study flow chart(s) / table of study procedures and assessments

See « Study Schedule » section.

9.2 Assessments of outcomes

9.2.1 Assessment of primary and secondary outcomes

The primary outcomes, the intensity and unpleasantness (emotional component) of pain experienced by patients during the PIC insertion, will be measured using a Visual Analog Scale (VAS) (Lang et al., 2014; Pagé et al., 2012). Patients' anxiety, as a secondary outcome, will also be measured by VAS. These three measurements will be performed by using three rulers after the PIC is inserted. These three rulers, with three different color codes to distinguish them, will be presented to the patients who will move the three sliders on a line going from one extreme to the other (No pain / Worst pain imaginable; Experience not at all unpleasant / Most unpleasant experience possible; Not at all anxious / Extremely anxious) and corresponding, on their other side, to a value between 0 and 100 mm on a 100 mm long line. This numerical value measured in millimetres will be reported in the CRF by the co-investigators. Patients will be asked to rate their overall feelings after the PIC insertion regarding these three aspects. The co-investigators will ensure that the caregivers do not become aware of the patients' responses.

As for caregivers' assessment of patients' pain intensity and unpleasantness and anxiety, these secondary outcomes will also be measured using the three VAS, this time in paper format and reported in the CRF after the PIC insertion. Caregivers will mark their estimation by tracing a line on each of the three VAS once they have completed their procedure, making sure that patients do not read their answers. The co-investigators will then measure the distance between the 0 extreme and the line traced by the caregivers in millimetres and report this numerical value in the CRF.

Before the PIC insertion, patients will assess the intensity and unpleasantness of any pre-existing pain and their basal anxiety level with these same three VAS. This will give a baseline value for these three measures. These values will be reported in the CRF before the PIC is inserted, along with the reason for consultation (internal medicine, traumatology or surgery) and any painkillers already given/ongoing in the ED.

Caregivers' behaviour will be assessed according to the criteria described by Kaptchuck (Kaptchuck et al., 2008) during the procedure. The algic behaviour of patients during the PIC insertion will also be evaluated using the Algoplus scale (Rat et al., 2011). These two behavioural evaluations will be the subject of a one-day « Rating » pilot phase, during which co-investigators will be asked to rate some of the same patients when a PIC is placed in order to ensure that their ratings are well correlated.

The characteristics of the procedure (location, caliber, number of attempts, difficulties and complications encountered), the demographic characteristics of the patients (sex, age, origin, level of education) and the demographic characteristics of the caregivers (sex, age) will be reported in the CRF after the PIC insertion. Patients will also be asked two questions (« Are you generally afraid of needles? », « Do you suffer from chronic pain, i.e. that has lasted for more than 3 months? ») to contextualize their VAS and chronic analgesics use will be reported.

Finally, in the second phase, a unique identifier related to the study (study number) will be assigned to each caregiver and entered in the CRF when the PIC is placed. If necessary, it will allow the data analysis by clustering patients by caregiver to account for the natural clustering of patients by caregivers and allow for a multi-level analysis of the caregiving effect. This identifier consisting of numbers and letters will be created from elements of the caregiver's personal identifiers that are not recognizable for a person who has not been involved in the study (e.g. D_F9B0). The identifying elements themselves will not be collected. The coding key for this study number will only be known to co-investigators collecting the data and the person in charge of monitoring the protocol. Caregivers themselves will only be informed of their code (not of the coding key). The principal investigator will not participate in data collection. When entering data into the Excel database, this study number will be coded again. That way, caregivers will not be identifiable for those performing the analysis (PI).

9.2.2 Assessment of safety outcomes

9.2.2.1 *Adverse events*

Any adverse event resulting from the intervention (i.e. procedural information), and not those arising from the reason for consultation in the ED, the care provided for this reason or the insertion of the PIC

(e.g. bleeding, hematoma), will be reported in the CRF and, if additional medical care has been required, reported to the CEC.

9.2.2.2 Laboratory parameters

Non-applicable.

9.2.2.3 Vital signs

Non-applicable.

9.2.3 Assessments in participants who prematurely stop the study

Participants who have revoked their consent or who are excluded from the study will have their data collected as part of the study destroyed, except for data relating to their sex and age, which will be kept for statistical purposes in a separate document (Appendices 7 and 8). They will be given a copy of the complete information sheet so that they can contact the investigators if they wish to do so.

9.3 Procedures at each visit

Non-applicable. Patients' participation in the study is unique. They will not be included in the first or second phase of the study if they are seen again in the ED.

10. SAFETY

As this study is part of a medical management context in an ED, adverse events resulting from the reason for consultation, the care provided for this reason or the PIC insertion (e.g. bleeding, hematoma) will not be reported as such in the CRF because they are independent of the study. Only adverse events directly resulting from the intervention (i.e. procedural information) will be reported in the CRF by the co-investigators and reported to the principal investigator within 2 hours. The CEC will also be informed within 2 days if preventive or corrective medical measures are necessary to protect the health and safety of the participants.

However, the risk of a specific adverse event for this very brief intervention that modulates only procedural information is very low or non-existent. Should any adverse event occur, it will be spontaneously reported in the CRF by the co-investigators during the intervention. In addition, participants will be actively questioned about any potential inconvenience to their participation during the debriefing phase. Finally, in order to ensure that any adverse events can also be reported after the end of the study, the complete information sheet containing the investigators contacts will also be handed out to all participants.

An annual safety report will be submitted to the CEC once a year.

11. STATISTICAL METHODS

This study aims to demonstrate the superiority of an information message with positive content on the pain felt when a PIC is applied. The power is set at 80% to demonstrate a difference, with an alpha threshold of 0.05.

11.1 Hypothesis

First null hypothesis: The recorded intervention message has an effect comparable to that of the recorded control message on the painful feeling induced by the insertion of a PIC.

First alternative hypothesis: The recorded intervention message reduces the intensity and unpleasantness of the pain induced by a PIC insertion of at least 13 mm from the recorded control message.

11.2 Determination of Sample Size

Based on a review of studies on pain during a PIC insertion (Baxter et al., 2009; Dutt-Gupta et al., 2007; Fossum et al., 2016; Fry et al., 2001; Hartstein et al., 2008; Kim et al., 2012; Marco et al., 2007; Ott et al., 2007), 2012; Soysal et al., 2005; Speirs et al., 2001; Witting et al., 2016), the mean pain intensity is estimated at 34 mm by the Visual Analog Scale (with a possible intensity between 0 and 100 mm), with a standard deviation estimated at 24 mm. To detect the smallest decrease in clinically significant pain intensity of 13 mm (Todd et al., 1996) due to the intervention, a sample of 110 patients, or 55 patients per arm, is required, with a power set at 80% and alpha set at 5%. Taking into account missing values or refusal to participate after randomization estimated at 10% of patients, 60 patients will be randomized per arm. A total of at least 240 patients will therefore be recruited for the two phases, i.e. the four arms, of the study.

11.3 Statistical criteria of termination of trial

Non-applicable.

11.4 Planned Analyses

Descriptive data will be presented by mean and standard deviation, median and interquartile space or proportions for Gaussian, non-Gaussian and categorical continuous variables. The comparison between randomized groups will be done by Student t-test or Wilcoxon rank sum test for continuous variables, and by Chi2 or Fisher for categorical variables, as appropriate.

The analyses will be performed using Stata software version 14 (StataCorp, TX, USA). The analysis will be performed by the principal investigator. To ensure that he is not aware of the assignment of patients to the intervention or control group, co-investigators will delete the patient number corresponding to that of the randomization list before the database is transmitted. Thus, the analysis of the data will be done blind. It is therefore a triple-blind study.

11.4.1 Datasets to be analysed, analysis populations

A first analysis will be made by « intention to treat ». Subsequently, a second « per protocol » analysis may address any differences between patients who received a complete or incomplete message in the second phase of the study.

11.4.2 Primary Analysis

The primary analysis will compare the pain intensity and unpleasantness after the PIC insertion as measured by VAS. The VAS will be compared by Student t-test if the distribution is Gaussian or by Wilcoxon rank sum test if not. The analysis will be conducted according to the « intention to treat » principle, which will include all randomized patients.

11.4.3 Secondary Analyses

The secondary analysis will compare the pain intensity and unpleasantness after the PIC insertion measured by VAS. The VAS will be compared by Student t-test if the distribution is Gaussian or by Wilcoxon rank sum test if not. The analysis will include only those patients for whom the message has been fully delivered.

The analysis of the secondary objectives, i.e. the intensity of anxiety, also measured by VAS, will focus on the comparison of VAS per Student t-test if the distribution is Gaussian or Wilcoxon rank sum

test if not. The same will be true for the caregivers' assessment by VAS of the patients' pain intensity and unpleasantness and anxiety level at PIC insertion.

11.4.4 Interim analyses

Non-applicable.

11.4.5 Safety analysis

Non-applicable.

11.4.6 Deviation(s) from the original statistical plan

Deviations from the original statistical analysis will be mentioned in the presentation of the results of the study, whether in the form of a Master's thesis or of a scientific paper.

11.5 Handling of missing data and drop-outs

Excluded patients or patients who have revoked their consent will be included in the calculation of the number of participants required to complete the collection of study data, but a 10% mark-up of this number is expected to compensate for these missing data.

For missing data other than the primary endpoint of judgment (pain intensity and unpleasantness after the PIC insertion), no imputation will be performed.

12. QUALITY ASSURANCE AND CONTROL

12.1 Data handling and record keeping / archiving

All data will be collected in paper format.

12.1.1 Case Report Forms

The patient's personal data will be treated by the co-investigators in a confidential and encrypted manner. A CRF (Appendices 4 and 5) and a document containing the patient's personal data (Appendix 6) will be established for each participant, who will be assigned an identification number in order to link these two documents. Only co-investigators will be authorised to complete the CRF and will certify it by signing at the end of each CRF. Any erasure/correction will be marked with the initials of the person making it. The two co-investigators, Anne Beyeler and Adélaïde Le Bloc'h, will make a double input of the CRF's data into the Excel database to ensure accurate input.

12.1.2 Specification of source documents

The source documents are the complete Patient Information Sheet and Consent Form (Appendices 2 and 3), the CRF (Appendices 4 and 5), the document containing the patient's personal data (Appendix 6), the documents prepared for patients who revoked their consent or were excluded from the study (Appendices 7 and 8), and the document containing the VAS reported by caregivers (Appendix 9).

All source documents will be stored in a secure room at the LUH and then in the principal investigator's office.

12.1.3 Record keeping / archiving

All collected data will be stored in the principal investigator's office for a period of 10 years after the planned or premature completion of the study.

12.2 Data management

The collected data will be entered anonymously into an Excel database. This computerized database will not contain any information identifying the source person. Only the two co-investigators, Anne Beyeler and Adélaïde Le Bloc'h, will be allowed to enter data into this Excel database. Double data entry will be made to ensure the accuracy of the data. If inconsistencies should arise as a result of this double entry, a follow-up of the changes will be set up for corrections. Data entry can only be made on the computer located in a LUH secure room and the Excel database will be protected by a password known only to the investigators. The database will be saved on an external hard drive that will remain in this LUH secure room until the data collection and entry is completed.

Once the data collection and entry is completed, the database will be deemed complete and cannot be modified. It can then be taken out of the LUH's secure room in order to be statistically analyzed by the principal investigator.

12.3 Monitoring

A research nurse in the LUH ED, will monitor this low-risk clinical trial. It is indeed classified in risk category A and there are no known risks associated with the intervention. Therefore, there will be a monitoring visit prior to the recruitment of the first participant, within one year of the start of the data collection and a closing visit after the end of the data collection.

The purpose of these visits will be to review the various documents and validate compliance with the protocol. The Monitor will verify the following variables for each patient included at the time of the visit: name, surname, first name, date of birth, sex, signed consent form, date of the intervention, message received, possible adverse reactions, main parameters collected (VAS). She will also verify that these variables have been correctly inserted in the database.

Visits will be scheduled according to the availability of each person and the date will be communicated to the co-investigators at least one week in advance. The co-investigators will be available to meet the Monitor and answer her questions. The monitor reserves the right to examine further documents and aspects of the study or to reschedule a visit if she deems it necessary.

If a problem is identified during these visits (e.g. poor coordination between co-investigators, missing documents), the Monitor will share it with the investigators and assist them in solving the problem.

12.4 Audits and Inspections

Study documents, including source documents, will be made available to the CEC or the competent authorities in the event of an audit. Investigators will respond to questions asked during the inspection.

12.5 Confidentiality, Data Protection

The CEC and the competent authorities will have direct access to source documents for monitoring, auditing or inspection. Investigators will have access to all study data except for the coding key for the caregiver study number in the second phase, which will only be known to co-investigators collecting the data and the Monitor. Only anonymised coded data, i.e. all data with the exception of documents containing patients' personal data and those containing the study number of the caregivers, may be made public.

12.6 Storage of biological material and related health data

Non-applicable.

13. PUBLICATION AND DISSEMINATION POLICY

The results of the study will be published in the form of a Master's thesis submitted to the School of Medicine, or in the form of a scientific article submitted for publication to peer-review journals.

14. FUNDING AND SUPPORT

The costs generated by this study will be covered by the Faculty of Biology and Medicine according to the expenses allocated for Master's thesis.

15. INSURANCE

In the event of any damage caused to the participants during this study, the LUH will be liable in its capacity as Sponsor in accordance with the applicable legal provisions.

16. REFERENCES

1. Declaration of Helsinki, Version October 2013, (<http://www.wma.net/en/30publications/10policies/b3/index.html>)
2. International Conference on Harmonization (ICH, 1996) E6 Guideline for Good Clinical Practice. (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf)
3. International Conference on Harmonization (ICH, 1997) E8 Guideline: General Considerations for Clinical Trials (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E8/Step4/E8__Guideline.pdf)
4. Loi fédérale relative à la recherche sur l'être humain (loi relative à la recherche sur l'être humain, LRH) du 30 septembre 2011. (<http://www.bag.admin.ch/themen/medizin/00701/00702/07558/index.html?lang=de>)
5. Ordonnance sur les essais cliniques dans le cadre de la recherche sur l'être humain (Ordonnance sur les essais cliniques, OClin) du 20 septembre 2013. (<http://www.bag.admin.ch/themen/medizin/00701/00702/12310/index.html?lang=de>)
6. Loi fédérale sur les médicaments et les dispositifs médicaux (Loi sur les produits thérapeutiques, LPT) du 15 décembre 2000. (<http://www.admin.ch/ch/d/sr/8/812.21.de.pdf>)
7. ISO 14155:2011 Clinical investigation of medical devices for human subjects -- Good clinical practice (www.iso.org)
8. ISO 10993 Biological evaluation of medical devices (www.iso.org)
9. WHO, International Clinical Trials Registry Platform (ICTRP) (<http://www.who.int/ictrp/en/>)

Académie Suisse des Sciences Médicales (ASSM). La communication dans la médecine au quotidien - Un guide pratique □ Brochure □. Bâle: Académie Suisse des Sciences Médicales; 2013. Disponible: <http://www.samw.ch/fr/Publications/Guides-pratiques.html>.

Baxter AL, Leong T, Mathew B. External thermomechanical stimulation versus vapocoolant for adult venipuncture pain: pilot data on a novel device. *Clin J Pain* 2009; 25(8): 705-10.

Dutt-Gupta J, Bown T, Cyna AM. Effect of communication on pain during intravenous cannulation: a randomized controlled trial. *Br J Anaesth* 2007; 99(6): 871- 5.

Fossum K, Love SL, April MD. Topical ethyl chloride to reduce pain associated with venous catheterization: a randomized crossover trial. *Am J Emerg Med* 2016; 34(5): 845-50.

Fry C, Aholt D. Local anesthesia prior to the insertion of peripherally inserted central catheters. *J Infus Nurs* 2001; 24(6): 404-8.

Greville-Harris M, Dieppe P. Bad is more powerful than good: the nocebo response in medical consultations. *Am J Med* 2015; 128(2): 126-9.

Hartstein BH, Barry JD. Mitigation of pain during intravenous catheter placement using a topical skin coolant in the emergency department. *Emerg Med J* 2008; 25(5): 257-61.

Kaptchuk TJ, Kelley JM, Conboy LA, Davis RB, Kerr CE, Jacobson EE, et al. Components of placebo effect: randomised controlled trial in patients with irritable bowel syndrome. *BMJ* 2008; 336(7651): 999-1003.

Kim S, Park K, Son B, Jeon Y. The effect of transcutaneous electrical nerve stimulation on pain during venous cannulation. *Curr Ther Res Clin Exp* 2012; 73(4-5): 134-9.

Krauss BS. « This may hurt »: predictions in procedural disclosure may do harm. *BMJ* 2015; 350: h649.

Lang EV, Benotsch EG, Fick LJ, Lutgendorf S, Berbaum ML, Berbaum KS, et al. Adjunctive non-pharmacological analgesia for invasive medical procedures: a randomised trial. *Lancet* 2000; 355(9214): 1486-90.

Lang EV, Hasiopoulou O, Koch T, Berbaum K, Lutgendorf S, Kettenmann E, et al. Can words hurt? Patient-provider interactions during invasive procedures. *Pain* 2005; 114(1-2): 303-9.

Lang EV, Tan G, Amihai I, Jensen MP. Analyzing acute procedural pain in clinical trials. *Pain* 2014; 155(7): 1365-73.

Li SF, Greenwald PW, Gennis P, Bijur PE, Gallagher EJ. Effect of age on acute pain perception of a standardized stimulus in the emergency department. *Ann Emerg Med* 2001; 38(6): 644-7.

Marco CA, Marco AP, Buderer NF, Jones JM. Pain perception among Emergency Department patients with headache: responses to standardized painful stimuli. *J Emerg Med* 2007; 32(1): 1-6.

Mistiaen P, Van Osch M, Van Vliet L, Howick J, Bishop FL, Di Blasi Z, et al. The effect of patient-practitioner communication on pain: a systematic review. *Eur J Pain* 2016; 20(5): 675-88.

Nevin K. Influence of sex on pain assessment and management. *Ann Emerg Med* 1996; 27(4): 424-6.

Ott J, Aust S, Nouri K, Promberger R. An everyday phrase may harm your patients: the influence of negative words on pain during venous blood sampling. *Clin J Pain* 2012; 28(4): 324-8.

Pagé MG, Katz J, Stinson J, Isaac L, Martin-Pichora AL, Campbell F. Validation of the numerical rating scale for pain intensity and unpleasantness in pediatric acute postoperative pain: sensitivity to change over time. *J Pain* 2012; 13(4): 359-69.

Rat P, Jouve E, Pickering G, Donnarel L, Nguyen L, Michel M, et al. Validation of an acute pain-behavior scale for older persons with inability to communicate verbally: Algoplus. *Eur J Pain* 2011; 15(2): 198.e1-198.e10.

Singer AJ, Richman PB, Kowalska A, Thode HC. Comparison of patient and practitioner assessments of pain from commonly performed emergency department procedures. *Ann Emerg Med* 1999; 33(6): 652-8.

Soysal S, Topacoglu H, Karcioğlu O, Serinken M, Koyuncu N, Sarikaya S. Factors affecting pain in intravenous catheter placement: role of depression illness. *Int J Clin Pract* 2005; 59(3): 276-80.

Speirs AF, Taylor KH, Joanes DN, Girdler NM. A randomised, double-blind, placebo-controlled, comparative study of topical skin analgesics and the anxiety and discomfort associated with venous cannulation. *Br Dent J* 2001; 190(8): 444-9.

Todd KH, Funk KG, Funk JP, Bonacci R. Clinical significance of reported changes in pain severity. *Ann Emerg Med* 1996; 27(4): 485-9.

Varelmann D, Pancaro C, Cappiello EC, Camann WR. Nocebo-induced hyperalgesia during local anesthetic injection. *Anesth Analg* 2010; 110(3): 868-70.

Wang F, Shen X, Xu S, Liu Y, Ma L, Zhao Q, et al. Negative words on surgical wards result in therapeutic failure of patient-controlled analgesia and further release of cortisol after abdominal surgeries. *Minerva Anesthesiol* 2008; 74(7-8): 353-65.

Wells RE, Kaptchuk TJ. To tell the truth, the whole truth, may do patients harm: the problem of the nocebo effect for informed consent. *Am J Bioeth* 2012; 12(3): 22-9.

Witting MD, Moayedi S, Yang Z, Mack CB. Advanced intravenous access: technique choices, pain scores, and failure rates in a local registry. *Am J Emerg Med* 2016; 34(3): 553-7).

17. APPENDICES

1. Template for Patient Partial Verbal Information
2. Complete Patient Information Sheet and Consent Form (1st phase)
3. Complete Patient Information Sheet and Consent Form (2nd phase)
4. CRF (1st phase)
5. CRF (2nd phase)
6. Patients' personal data
7. Data (sex and age) of patients who revoked their consent
8. Data (sex and age) of patients excluded from the study
9. Caregivers' VAS