EINE ABTEILUNG DER SPITALSPARTNER BRÜDER. SCHWESTERN. LINZ

[redacted]

CLINICAL STUDY PROTOCOL

A prospective, randomized, double-blind, controlled trial on the application of a 10%-lidocaine spray prior to the insertion of a peripheral intra-venous catheter in female adults

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Sponsor: Ordensklinikum Linz

Inhalt

1. Study Synopsis English

Title

A prospective, randomized, double-blind, controlled trial on the application of a 10%-lidocaine spray prior to the insertion of a peripheral venous catheter in female adults.

Short Title

VENLID

Name of Medication

10% Lidocaine Spray

Description of procedures

Volunteers are invited to undergo 4 insertions of a peripheral intra-venous 18-gauge catheter (PIVC); 2 insertions at the the start of the study on the plantar side of the hand/vessel at the dorsum manus, 2 insertions after 2-10 hours into the forearm/cubita with and without application of a 10-% lidocaine spray (5 hubs of xylocaine 10%-pump spray; AstraZeneca BV, Zoetermeer, The Netherlands) prior to the insertion of the PIVC.

Objectives

Primary objective:

- To demonstrate a reduction of pain caused by PIVC rated by Numerical Rating Scale (NRS), after application of a 10% lidocaine spray- Separately measured for the plantar side of the hand/vessel at the dorsum manus, and for the forearm/cubita.

Secondary objectives:

- To measure pain caused by PIVC rated by NRS in the dominant vs. non-dominant arm
- To measure pain caused by PIVC rated by NRS at the plantar side of the hand/vessel at the dorsum manus, vs. at the forearm/cubita
- To measure the correlation between pain caused by PIVC rated by NRS and the anticipated pain rated by NRS

- To measure the correlation between pain caused by PIVC rated by NRS and the anticipated difficulty by the operator to insert the PIVC
- To measure pain rated by NRS depending on success
- To describe success rates and compare it
- To measure the correlation between PCS and pain caused by PIVC rated by NRS

Type of investigation

A prospective, randomized, double-blind, single-center study

Number of patients

40 volunteers- 80 upper extremities

Inclusion criteria

Female volunteers 18-45 years (we choose female volunteers because only femal patients are treated at the department of gynecology and obstetrics)

Personal history of ever having a venipuncture or insertion of PIVC

Exclusion criteria

Fractures on the upper extremity resulting in permanent movement restriction

Significant burns on the upper extremity-at the discretion of the principal investgator

Personal history of any thrombosis

Personal history of chemotherapy

Potential allergy to a PIVC

Personal history of surgery in the axilla

Personal history of any pathologies in the blood coagulation pathway

Personal history of difficult peripheral venous access

Personal history of complications with a PIVC

Any concomitant use of an analgesic within the previous 24 h

Any concomitant use of anticoagulation

Primary Endpoint

Pain caused by PIVC rated by NRS separately for the back of the plantar side of the hand/vessel at the dorsum manus, and for the forearm/cubita.

Secondary Endpoints

1. Pain caused by PIVC in the dominant vs. non-dominant arm
2. Pain caused by PIVC at the plantar side of the hand/vessel at the dorsum manus, vs. at the forearm/cubita
3. Correlation between pain caused by PIVC and the anticipated pain
4. Correlation between pain caused by PIVC and the anticipated difficulty by the operator to insert the PIVC
5. Success rate of the venepuncture by descriptive analysis and comparison
6. Pain caused by PIVC broken down by success/failure of insertion of PIVC
7. Correlation between pain caused by PIVC and PCS
8.

Statistics

Primary Endpoint: paired t-test of pain caused by PIVC rated by NRS with/without LA separately for the plantar side of the hand/vessel at the dorsum manus, and the forearm/cubita.

Null hypothesis

There is no difference in pain with and without application of LA for the plantar side of the hand/vessel at the dorsum manus.
There is no difference in pain with and without application of LA for the forearm/cubita.

Alternative hypothesis

There is a difference in pain with and without application of LA for the plantar side of the hand/vessel at the dorsum manus, and the forearm/cubita.

Table 1. Visit Schedule

Visit	1	2
Name	Screening	Treatment Day
Time		Day 1
Informed Consent	X	
Inclusion/Exclusion Criteria	X	
Medical History	X	
Urine pregnancy test	X	
PIVC vessel at the dorsum manus		X
PIVC forearm/cubita		X

2. INTRODUCTION

Background information

Insertion of a peripheral intra-venous catheter (PIVC) is one of the most common medical procedures worldwide (Webster et al., 2019; Helm et al., 2015; Zingg et al. 2017; Hadaway et al., 2012; Zingg et al., 2023). While many studies focused on potential short and long term complications of PIVC such as phlebitis, infiltration/extravasation, occlusion, leakage, and dislodgement (Marsh et al., 2020; , Lv et al., 2020; Messika et al., 2015; Maki et al., 2006; Worth et al., 2018) and pain in children (Cozzi et al., 2022), few studies have adressed pain and discomfort in adults.

Recently, pain caused by the application of PIVC has gained more attention in the scientific literature (Bond et al., 2016). It has also been stated that causing unnecessary pain during medical procedures - including insertion of peripheral PIVC - is doing harm to the patients (Bond et al., 2016; Selby et al., 1995). A meta-analysis compared the pain after a local anesthetic with the unattenuated pain of PIVC insertion and found that all applications of local anaesthetic were less painful than PIVC insertion without the local anesthetic (Bond et al., 2016). The authors concluded that applying a local anesthetic prior to PIVC insertion should become standard practice and should be seen as a surrogate marker of high-quality care (Bond et al., 2016). Potentially unnecesary pain is uncomfortable for the patient and may also increase fear and anxiety about future treatments (Joshi et al., 2005; Moore et al., 2009; Pfingsten et al., 2004; Todd et al., 1991). Pain may also trigger an autonomic nerve response resulting in vasoconstriction (Calder et al., 2007; Bamgbade et al., 2007) potentially making PIVC more difficult to insert (Collignon et al., 1994; Kagel et al., 2004; Maki et al., 2006).

Practice patterns concerning the use of local anesthesia prior ro insertion ov PVC are differing widely (Sado et al., 2005). .Usually local anaesthesia is only provided for children prior to PIVC (Cozzi et al., 2022, Bond et al., 2016). Mostly, intradermally injected lidocaine, a eutectic cream consisting of a mixture of local anesthetics (EMLA®), or a

vapocoolant spray are being used. Local anesthesia is rarely offered to adults due to an assumed low grade of pain. Caregivers report various reasons for this, including that it was time-consuming (45 %), not indicated (35 %), made PIVC more difficult (21 %), not available (13 %), logistically difficult (13 %), against peer pressure (4 %), not allowed (4 %) and practically difficult (4 %) (Norris et al., 2002).

While many local anesthetic procedures either take a rather long preparation time, such as EMLA or cause pain by itself such as intradermal injection of lidocaine, lidocaine spray is an easy to use and readily available agent, which has been used for various indications and only needs a short exposure time. (Kanai et al., 2009; Evans et al., 2006; Tanaka et al., 2015; Sunkareni et al., 2011). Its effects reportedly begin within 1–2 min, reach maximum efficacy within 5 min, and last for approximately 15min (Lee et al., 2016). Studies have shown that lidocaine spray is successful in reducing pain from cervical traction during intrauterine device placement, endometrial sampling, nasoenteral catheterization, and arteriovenous fistula manipulation (Torky et al., 2017; Karasu et al., 2017; Aksoy et al., 2016; de Oliveira et al., 2020; Song et al., 2016).

Regarding venous punctures, lidocaine spray has been successfully tested prior to the insertion of a non-coring needle into a totally implantable venous access port (Zhu et al., 2023), in patients administered a contrast medium during vein puncture (Oh et al., 2016) and in radial arterial puncture (Yildiz et al., 2021). It can be assumed that local anesthesia in general and lidocaine spray in particular can reduce pain in the range of 10mm on the Visual Analogue Scale or one point in the Numeric Rating Scale (NRS). This reduction of pain has also been reported to be of clinical relevance (Rüsch et al., 2017)

Interestingly, only two small randomized study have been published on lidocaine spray prior to insertion of a PIVC; one with a relatively low number of patients using only a 20 gauge PIVC. It is not unexpected that in this scenario the application of lidocaine spray does not reduce pain

levels (Datema et al., 2019). The other study reports positive findings with the lidocaine spray significantly reducing venipuncture-associated pain. Of note, a 20 minute waiting time time prior to the venipuncture was used in this study (Van Straten et al., 2018).

Therefore, the aim of the present study is to provide clinically important data on local anesthetic application prior to PIVC insertion with a short exposure time. If positive, these data are likely to change clinical practice.

Rationale of the clinical investigation

Promising data have been reported on local anesthesia prior to PIVC insertion. Our treatment plan aims at making local anesthesia application prior to PIVC clinically feasible as we test a 2 min exposure time to local anesthesia with a readily available and well known local anesthesia preparation.

3. OBJECTIVES OF THE CLINICAL INVESTIGATION (HYPOTHESIS)

Objectives (Hypothesis)

Primary objective:

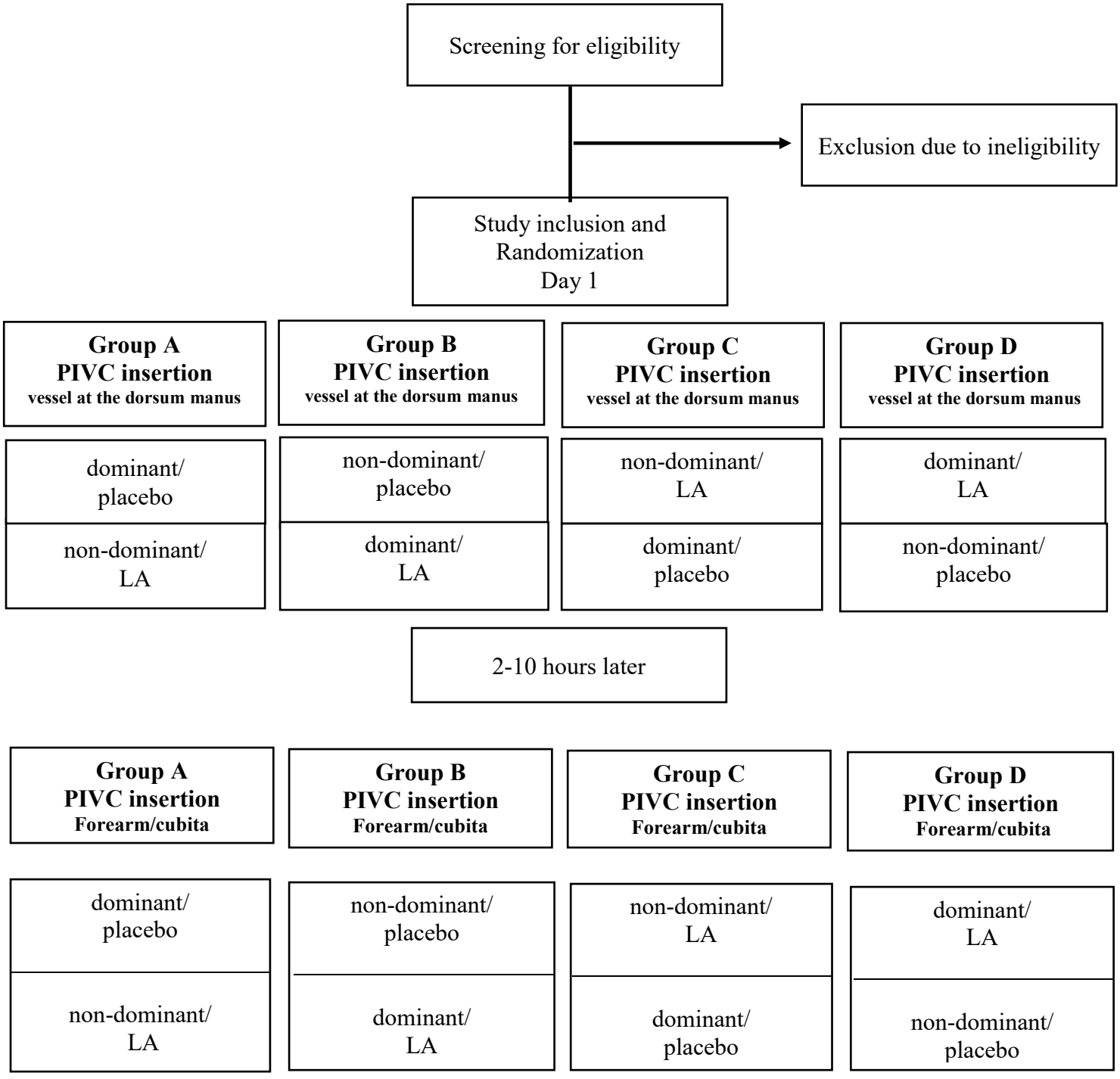
- To demonstrate a reduction of pain caused by PIVC rated by Numerical Rating Scale (NRS), after application of a 10% lidocaine spray- Separately measured for the plantar side of the hand/vessel at the dorsum manus, and for the forearm/cubita.

Secondary objectives:

- To measure pain caused by PIVC rated by NRS in the dominant vs. non-dominant arm
- To measure pain caused by PIVC rated by NRS at the plantar side of the hand/vessel at the dorsum manus vs. at the forearm/cubita
- To measure the correlation between pain caused by PIVC rated by NRS and the anticipated pain rated by NRS
- To measure the correlation between pain caused by PIVC rated by NRS and the anticipated difficulty by the operator to insert the PIVC

- To measure pain rated by NRS depending on success
- To describe success rates and compare it
- To measure the correlation between PCS and pain caused by PVIC rated by NRS

4. Study protocol and design Figure 1



Screening

All volunteers are screenend for study participation, a medical history is taken, inclusion/exclusion criteria are checked, a urine pregnancy test is performed. A respective informed consent is signed.

Treatment day 1:

First, volunteers will undergo insertion of PIVC into the vessel at the dorsum manus; Volunteers are randomized in 4 groups, volunteers serve as there own controls-see Figure 1
2-10 hours later:
All volunteers will undergo insertion of PIVC into the forearm/cubita, volunteers serve as their own controls.

Description of Randomization.

4 randomization groups are defined per protocol.

"Dominant" refers to the stronger hand/forearm.

o Group A: dominant/Placebo – non-dominant/LA
o Group B: non-dominant/Placebo – dominant/LA
o Group C: non-dominant/LA – dominant/Placebo
o Group D: dominant/LA – non-dominant/Placebo

Four bottles (a,b,c,d) are prepared by the pharmacy. Two bottles are filled with placebo and two bottles with the local anesthetic. The content of these bottles are only known by the Sponsor and the pharmacy.

Bottle a= local anesthetic (vessel at the dorsum manus)
Bottle b= placebo (vessel at the dorsum manus)
Bottle c= placebo (forearm/cubita)

Bottle d= local anesthetic (forearm/cubita)

On the treatment day the subinvestigator will obtain a card for each subject in which the treatment for each subject is specified. There are 40 cards and each card specifies the treatment protocol for a single subject. See attached document 2023-507859-29 Randomization cards.

Neither the subinvestigator nor the subjects will know what the content of the bottles are.

The plantar side of the hand and the forearm/cubita are randomized separately into the four groups A,B,C,D. Afterwards hand and arm are combined with each other. See attached document 2023-507859-29 Randomization key.

Randomization lists were generated via two separate block-randomization, one for hand and one for forearm.
Two separate block randomizations are forseen for the plantar side of the hand/vessel at the dorsum manus and for forearm/cubita via Software R version 4.2.2 (R Core Team, 2022) and Package blockrand version 1.5 (Snow, 2020). Each 2 blocks with a block length of 20 leading to 40 subjects randomized with the same amount to 4 groups.
This resulting list is only accessible for the sponsor.
Only the principal investigator will be accountable for the medication and placebo throughout the study and knows how the numbers are assigned to the groups.

5. Study population

It is planned to include 40 healthy female volunteers into this trial.

Inclusion criteria

Female probands 18-45 years

Personal history of ever having a venipuncture or insertion of PIVC

Exclusion criteria

Fractures on the upper extremity resulting in permanent movement restriction

Significant burns on the upper extremity-at the dirscretion oft he principal investgator

Personal history of any thrombosis

Personal history of chemotherapy

Potential allergy to a PIVC

Personal history of surgery in the axilla

Personal history of any pathologies in the blood coagulation pathway

Personal history of difficult peripheral venous access

Personal history of complications with a PIVC

Any concomitant use of an analgesic within the previous 24 h

Any concomitant use of anticoagulation

Pregnancy

Females of childbearing potential

Pregnant or breast-feeding women are excluded form study participation.

Duration of the clinical investigation

Max. 10 hours

Withdrawal and replacement of subjects

Criteria for withdrawal

Subjects may prematurely discontinue from trial participation at any time without having to give any reason. Premature discontinuation from trial participation is to be understood when the subject did not all 4 insertions of PIVC on the same day.

Subjects must be withdrawn under the following circumstances:

- at their own request
- if the investigator feels it would not be in the best interest of the subject to continue
- if the subject violates conditions laid out in the consent form / information sheet or
- disregards instructions by the clinical investigation personal

In all cases, the reason why subjects are withdrawn must be recorded in detail in the CRF and in the subject's medical records. Should the clinical investigation be discontinued prematurely, all clinical investigation materials (complete, partially completed and empty CRFs) will be retained.

Follow-up of patients withdrawn from the clinical investigation
No follow-up will be performed.

Replacement policy
No replacement of volunteers will be performed.

Premature termination of the clinical investigation

The sponsor has the right to close this clinical investigation at any time. The independent ethics committee (IEC) and the competent regulatory authority must be informed immediately.
The clinical investigation will be terminated prematurely in the following cases:

- If adverse event/adverse devise effect occur which are rendered so serious that the risk-benefit ratio is inacceptable.
- If the number of dropouts is so high that proper completion of the clinical investigation cannot be expected.

6. Methodology

Treatment duration and modification

The study duration for each individual volunteer is estimated to be 4-10 hours. A group of 5 residents working at the department of Obstetrics and Gynecology, Ordensklinikum Linz/BHB Linz are selected as potentially being responsible for inserting the PIVC; these are numbered in alphabetical order; a random number between 1 to 5 is generated by and the respectice resident is chosen as being responsible for inserting the PIVC.

Medication

Lidocaine spray 10 % (Xylocaine 10% pump spray; AstraZeneca BV, Zoetermeer, The Netherlands) and the placebo, physiological saline solution (NaCl 0,9% 250ml Fresenius KABI), are filled in neutral brown glass bottles with a dispenser dispensing 0.1ml per pulse of the dispenser by the Pharmacy of the Konventhospital Barmherzige Brüder Linz on the basis of AMG.
Lidocaine spray 10 % (Xylocaine 10% pump spray) and the placebo (physiological saline solution NaCl 0,9%), are filled in neutral brown glass bottles. 2 bottles each are available. 2 bottles with label "a" and "b" for plantar side of hand/vessel at the dorsum manus and 2 bottles with label "c" and "d" for forearm/cubita. One of the bottles "a" and "b" is a placebo and the other one the local anaesthetic. One of the bottles "c" and "d" is a placebo and the other one the local anaesthetic.

The person responsible for PIVC insertion and the volunteers are unaware which bottle contains the 10% lidocaine and which bottle the saline solution. Due to the banana like smell of lidocaine the person responsible for PIVC insertion and the volunteer will wear nose clips during the procedure.

Accountability of the medication

The principle investigator will be accountable for the medication and placebo throughout the study.

Intended Use

Lidocaine spray 10 % is applied with a dispenser dispensing 0.1ml per pulse of the dispenser on the area of the skin, where the insertion of the PIVC is planned. Exposure time is 2 min, timed with an hour glass; validated prior to the study by a stop watch. 0.5 ml (5 pulses) of 10% lidocaine spray (equals 50mg of lidocaine) are to be applied before insertion of a PIVC 18 Gauge.

Null hypothesis:

There is no difference in pain with and without application of LA for the plantar side of the hand/vessel at the dorsum manus.

There is no difference in pain with and without application of LA for the forearm/cubita.

Alternative hypothesis:

There is a difference in pain with and without application of LA for the plantar side of the hand/vessel at the dorsum manus, and the forearm/cubita.

Type I and II errors

α 5% two-sided

β 20%

Statistics

Pain caused by PIVC rated by NRS with/without application of local anesthesia will be analyzed by a paired- t-test. NRS is used as a continuous measure and we expect the values to be approximately

normally distributed and therefore plan a parametric test. Normal distribution will be investigated via Shapiro-Wilk-Test. If there is no normal distribution, the non-parametric Wilcoxon test for paired samples will be used instead of the paired t-test. For descriptive analyses, mean values and standard deviations will be reported. For each primary outcome (plantar side of the hand/vessel at the dorsum manus and the forearm) separate significance tests for separate null hypotheses will be calculated and no adaption of the error due to multiple testing is needed. The analysis will be performed with the SPSS software (SPSS 32.0, SPSS Inc., Chicago, IL).
For the analysis of the secondary endpoints paired t-test, independent t-tests and pearson correlation will be used. If the data is not normal distributed, wilcoxon test for paired samples, Mann-Whitney-U test for independent samples and spearman correlation will be employed instead. For analyzing the success rate a chi-squared test will be calculated for comparison of groups.

Randomization is performed by a standard randomization program; groups are stratified by where (dominant vs. non-dominant extremity) the first PIVC will be inserted and whether LA or placebo is used at the first PIVC insertion resulting in 4 distinct groups.

No effect of order of dominant/non-dominant and placebo/LA is expected and thus in the main statistical analysis (see above) the randomization will not be taken into account. Nevertheless, an additional statistical analysis will be run as sensitivity analysis where the both randomization factors will be used as control variables in an ANOVA model.

Sample size

Sample size calculation was done using G*Power 3.1 (Faul et al. 2007) based on the main statistical analysis, the paired t-test, with a two-sided level of significance of 5 % and a power of 80 %. An effect size measure

of Cohens d = 0.5 is used as this represents a difference in means of 1 unit and a standard deviation of 2 and refers to a medium sized effect (Cohen 1988). The sample size calculation resulted in a required sample size of 36 for the analysis. As a drop out of 10 % is assumed, a sample size of **40** for the study is needed.
An internal survey of 20 doctors at our department revealed an assumed drop out rate of 10%.

Specific safety monitoring: Side effects of the treatment will be monitored and documented immediately after the treatment and during all follow up visits.

Concomitant medication

There is no need to change of concomitant medication.

Interactions, reverse reactions and side effects

Side effects of Lidocaine 10% on the skin:
Often (that is, one to ten percent of those treated) temporary skin irritation and redness.
Rarely (in less tahn 0.1 percent of thode treated) allergic reactions, severe itching on the skin /with raised lumps.
Side effects of the treatment will be monitored and documented immediately.

Benefit and risk assessment

Benefits of volunteers
Volunteers will receive a compensation for missing work for one day and compensation for pain and inconvenience, i.e. 140 Euro.

Risk of the volunteers

Volunteers will experience light to moderate pain by the insertion of the PIVC. Typical side effects of insertion of a PIVC include hematoma, bleeding, arterial punction, phlebitis, thrombosis, infection, abscesses, lacerating nerves, pain, etc. As the PIVC is inserted by an experienced operator, a standard operating procedure is followed, the PIVC will be immediately removed after insertion, all volunteers are monitored by a physician, PIVC insertion is performed within a hospital, and all volunteers know what to expect; the risk of study participation is regarded as minimal.

Clinical investigation procedures

All study-related measures will be performed at Ordensklinikum Linz /Konventhospital der Barmherzigen Brüder Linz. Volunteers are asked to lie comfortably horizontally on a bed with the head on a pillow. A tourniquet is put around the upper arm, tightened, and the site of the venipuncture is identified; the operator rates the anticipated difficulty of the PIVC insertion by NRS. The volunteer is asked to rate her anticipated pain by NRS and the fill in the **Pain Catastrophizing Scale (PCS).**

The PCS is a self-assessment questionnaire to examine catastrophizing in clinical and nonclinical populations (Suren et al., 2014). Catastrophizing is commonly described as an exaggerated negative orientation toward noxious stimuli and plays an important role in experiencing and coping with pain. The PCS consists of 13 statements containing a number of thoughts and feelings one may experience when having pain. The items are divided into the categories of rumination, magnification and helplessness, with each item scored on a 5-point scale. Wheeler et al. report a mean test–retest reliability of 0.88 (95% CI 5 0.83-0.93, range 0.73-0.97), representing good reliability. Internal consistency as expressed with Cronbach’s alpha was 0.92 (95% CI 5 0.91-0.93) for the full scale, 0.89 (95% CI 5 0.87-0.91) for the rumination

subscale, 0.77 (95% CI 5 0.73-0.82) for the magnification subscale and 0.88 (95% CI 5 0.86-0.9) for the helplessness subscale. Using a 5-point Likert scale, from 0 (not at all) to 4 (always), people are asked to rate how often they experience the mentioned thoughts and feelings when they are in pain. Along with three subscale scores evaluating rumination, magnification, and helplessness, the overall score has a range of 0-52.

Subscale Scores: Rumination: Items 8,9,10,11; Magnification: Items 6,7,13; Helplessness: Items 1,2,3,4,5,12

Higher scores indicate a greater degree of pain catastrophizing. A total score of >30 represents a clinically significant level of pain catastrophization.

Lidocaine spray 10 % and the placebo, physiological saline solution, are filled in neutral brown glas bottles with a dispenser dispensing 0.1ml per pulse of the dispenser by the Pharmacy of the Konventhospital Bermherzige Brüder Linz, The operator and the volunteers are unaware which bottle contains the 10% lidocaine and which bottle the saline solution. 5 pulses of either lidocaine 10% or saline are applied to the site of the planned venipuncture (plantar side of the hand/vessel at the dorsum manus), an hourglass indicating the 2 min time is turned. The tourniquet is then loosened. After 2 minutes the tourniquet is tightened agained, desinfection is performed, another 30 sec is waited-timed by an hourglass-and the insertion of the PIVC is performed. The following PIVC will be used: BD Venflon Pro Safety, BD Vialon Material; 18G 1.3 x 32 mm; (Beckton Dickinson Therapy, Helsingborg, Sweden). To check for success of the insertion of the PIVC 5 ml of saline is injected; either way (success/failure) the PIVC is to be removed and the pain caused by PIVC rated by NRS is recorded. A pressure bandage will be applied and the volunteer is checked for well being and discharged at the principal investigator’s discretion. Then the same procedure is repeated on the other extremity.

After 2-10 hours the next two insertions are performed according to the above mentioned protocol on the forearm/or within the cubita. Afterwards the volunteers are checked for well-being.

General rules for clinical investigation procedures

All clinical investigation measures (vital parameters, ECG, etc.) have to be documented with the current day and time.

The dates of all procedures should be according to the study protocol. The time margins mentioned in the clinical investigation flow chart are admissible. If for any reason, a clinical investigation procedure is not performed within scheduled margins a protocol deviation should be noted, and the procedure should be performed as soon as possible or as adequate.

7. Safety definitions and reporting requirements

Adverse event (AE):

Summary of known and potential risks of the medical device

Side effects that might occurr during the approximately three-minute insertion process of the PIVC are pain, syncope, bleeding, and allergic reaction to lidocaine.

Definition of adverse event and adverse device effect

An Adverse Event (AE) is any adverse change from the subject's baseline condition, i.e. any unfavorable and unintended sign including an abnormal laboratory finding, symptom or disease which is considered to be clinically relevant by the physician that occurs during the course of the study, whether or not considered related to the medical device.

Adverse event includes:

Exacerbation of a pre-existing disease.

Increase in frequency or intensity of a pre-existing episodic disease or medical condition.
Disease or medical condition detected or diagnosed after treatment with the medical device even though it may have been present prior to the start of the clinical investigation.
Continuous persistent disease or symptoms present at baseline that worsen following the start of the clinical investigation.
Lack of efficacy in the acute treatment of a life-threatening disease.
Events considered by the investigator to be related to clinical investigation-mandated procedures.
Abnormal assessments, e.g., ECG and physical examination findings, must be reported as AEs if they represent a clinically significant finding that was not present at baseline or worsened during the course of the clinical investigation.
Laboratory test abnormalities must be reported as AEs if they represent a clinically significant finding, symptomatic or not, which was not present at baseline or worsened during the course of the clinical investigation lead to interruption or permanent discontinuation of medical device.

Adverse events do not include:
Pre-planned interventions or occurrence of endpoints specified in the study protocol are not considered AEs, if not defined otherwise.
Medical or surgical procedure, e.g. surgery, endoscopy, tooth extraction, transfusion.
However, the event leading to the procedure is an AE. If this event is serious, the procedure must be described in the SAE narrative.
Pre-existing disease or medical condition that does not worsen.
Situations in which an adverse change did not occur, e.g., hospitalizations for cosmetic elective surgery or for social and/or convenience reasons.
Misuse of either medical device or concomitant medication without any signs or symptoms. However, misuse must be mentioned in the Medical Device Inventory/ Treatment Log.

Serious adverse event (SAE)

A Serious Adverse Event (SAE) is defined as any AE fulfilling at least one of the following criteria:

A) leads to a death,

B) leads to a serious deterioration in the health of the subject that

1. resulted in a life-threatening illness or injury,
2. resulted in a permanent impairment of a body structure or a body function,
3. required in-patient hospitalization or prolongation of existing hospitalization,

C) is an important medical event that may not immediately result in death, be life-threatening, or require hospitalization but may be considered as SAEs when, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions above.

D) shows the occurrence of a malignant tumor (§3 (16) MPG).

Life-threatening refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

Hospitalization – Prolongation of existing hospitalization
Hospitalization is defined as an overnight stay in a hospital unit and/or emergency room. An additional overnight stay defines a prolongation of existing hospitalization.
The following is not considered an SAE and should be reported as an AE only:

- Treatment on an emergency or out subject basis for an event not fulfilling the definition of seriousness given above and not resulting in hospitalization.

The following reasons for hospitalizations are not considered AEs, and therefore not SAEs:
Hospitalizations for cosmetic elective surgery, social and/or convenience reasons.
Standard monitoring of a pre-existing disease or medical condition that did not worsen, e.g., hospitalization for coronary angiography in a subject with stable angina pectoris.
Elective treatment of a pre-existing disease or medical condition that did not worsen, e.g., hospitalization for chemotherapy for cancer, elective hip replacement for arthrosis.

SAE related to investigational drug

Such SAEs are defined as SAEs that appear to have a reasonable possibility of causal relationship.

Reporting procedure of SAEs

In case of a serious adverse event, the Investigator has to use all supportive measures for best patient treatment.
Reporting needs to follow the rules laid down in Article 41 of Regulation (EU) 536/2014 and Annex III. The investigator shall report serious adverse events to the sponsor without undue delay but not later than within 24 hours of obtaining knowledge of the events.
A written report is also to be prepared and should at least contain the following:

- Patient number
- Patient sex
- The suspected investigational medical product (IMP)
- The adverse event assessed as serious
- Short description of the event and outcome If applicable, the initial report should be followed by the Follow up report, indicating the outcome of the SAE.

ADR adverse drug reaction is a "response to a drug which in noxious and unintended and which occurs at doses normally used in a man for prophylaxix, diagnosis, or therapy of disease or for the modification of physiologic function". An ADR is harm directly caused by the drug at normal doses, during normal use. An ADR is a special type of AE in which a causative relationship can be shown.

SUSARS Suspected unexpected Serious Adverse Reaction

SUSARs are all serious adverse reactions with suspected causal relationship to the study drug that is unexpected (not previously described in the Summary of Product Characteristics or Investigator's brochure) and serious.

Reporting procedures of SUSARs

Reporting needs to follow the rules laid down in Article 42 of Regulation (EU) 536/2014 and Annex III.

The period for the reporting of suspected unexpected serious adverse reactions by the sponsor to the Agency shall take account of the seriousness of the reaction and shall be as follows:

(a) in the case of fatal or life-threatening suspected unexpected serious adverse reactions, as soon as possible and in any event not later than seven days after the sponsor became aware of the reaction

(b) in the case of non-fatal or non-life-threatening suspected unexpected serious adverse reactions, not later than 15 days after the sponsor became aware of the reaction

(c) in the case of a suspected unexpected serious adverse reaction which was initially considered to be non-fatal or non-life threatening but which turns out to be fatal or life-threatening, as soon as possible and in any event not later than seven days after the sponsor became aware of the reaction being fatal or life-threatening.

Where necessary to ensure timely reporting, the sponsor may, in accordance with section 2.4 of Annex III, submit an initial incomplete report followed up by a complete report.
Such reports shall be made by the sponsor and should content at least the following details:

- Patient number (study code/screening number)
- Patient age in years and sex
- Name of Investigator and investigating site
- Period of administration
- The suspected investigational medical product (IMP)
- The adverse event assessed as serious and unexpected, and for which there is a suspected causal relationship to the IMP
- Concomitant disease and medication
- Short description of the event:
- Description
- Onset and if applicable, end
- Therapeutic intervention
- Causal relationship
- Seriousness criteria or reportable reason

Electronic reporting to the database referred to in Article 40 (1) of Regulation (EU) 536/2014 ("Eudravigilance") should be the expected method for reporting of SUSARs to the competent authority. In that case, the format and content as defined by the regulatory requirements should be adhered to. The latest version of MedDRA should be applied. Lower level terms (LLT) should be used.

The written report is divided into two parts:

- Initial report: Informs about what has happened (AE assessed as serious), if there is a relationship to the medical device, and which action was set.
- Follow up-Report: informs about the outcome

The Sponsor is responsible for the classification of adverse events and ongoing safety evaluation of the clinical investigation and shall:

- review the investigators assessment of all adverse events and determine and document in writing their seriousness and relationship to the investigational device
- review all devices deficiencies and determine and document in writing whether they could have led to a serious adverse device effect

Developmet safety udate report

A Development Safety Update Report (DSUR) will be provided by the Sponsor annually in accordance with Article 43 of Regulation (EU) 536/2014 and the ICH E2F guidance document.

This report will be submitted to the National Competent Authorities and Ethics Committees via the electronic system referred to in Articles 80 of Regulation (EU) 536/2014 ("Clinical Trials Information System, CTIS").

Severity of adverse events

The severity of clinical AEs is graded on a three-point scale: mild, moderate, severe, and reported on specific AE pages of the CRF.

If the severity of an AE worsens during medical device administration, only the worst intensity should be reported on the AE page. If the AE lessens in intensity, no change in the severity is required.

Mild

Event may be noticeable to subject; does not influence daily activities; the AE resolves spontaneously or may require minimal therapeutic intervention;

Moderate

Event may make subject uncomfortable; performance of daily activities may be influenced; intervention may be needed; the AE produces no sequelae.

Severe

Event may cause noticeable discomfort; usually interferes with daily activities; subject may not be able to continue in the study; the AE produces sequelae, which require prolonged therapeutic intervention.
A mild, moderate or severe AE may or may not be serious. These terms are used to describe the intensity of a specific event (as in mild, moderate, or severe myocardial infarction). However, a severe event may be of relatively minor medical significance (such as severe headache) and is not necessarily serious. For example, nausea lasting several hours may be rated as severe, but may not be clinically serious. Fever of 39°C that is not considered severe may become serious if it prolongs hospital discharge by a day. Seriousness rather than severity serves as a guide for defining regulatory reporting obligations.

Relationship to the study procedures

For all, the investigator will assess the causal relationship between the study procedures and the AE using his/her clinical expertise and judgment according to the following algorithm that best fits the circumstances of the

AE:

Unrelated

May or may not follow a reasonable temporal sequence from administration of the study product
Is biologically implausible and does not follow known response pattern to the suspect medical device (if response pattern is previously known)

Can be explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.

Unlikely

There is a reasonable temporal relation between the AE and the medical device, but there is a plausible other explanation for the occurrence of the AE.

Possibly

Follows a reasonable temporal sequence from administration of the medical device.

The AE may equally be explained by the study subject's clinically state, environmental ortoxic factors, or concomitant therapy administered to the studsubject.

- The relationship between the medical device and AE may also be clinically plausible.

Probably

Follows a reasonable temporal sequence from administration of the medical device, and plausible reasons point to a causal relation with the medical device.

Related

Follows a reasonable temporal sequence form administration of the medical device.

Follows a known response pattern to the medical device (if response pattern is previously known).

No other reasonable cause is present.

Not assessable

The causal relationship between the medical device and the AE cannot be judged.

- report or ensure the reporting of all SAEs, wheter or not related to the medical device, to the EC and regulatory authorities (AGES)!

8. Follow Up

Follow-up of clinical investigation participants including follow-up of adverse events

No follow up will be performed.

9. STATISTICAL METHODOLOGY AND ANALYSIS

Intention to treat set

The statistical analysis of the primary and secondary endpoint is based on the intention-to-treat principles i.e. all patients included in the study will be analyzed.

Sample size

Sample size see section 7. Methodology

Relevant protocol deviations

All study protocol deviations will be listed in the study report. No deviations from the study protocol of any type will be made without complying with all IRB/EC established procedures and in accordance with applicable regulations.

Statistical analysis plan

A statistical analysis plan (SAP) will be completed before closure of the database. The SAP will include precise information on the statistical tests and the descriptive calculations for primary and secondary endpoints that will be used, the exact specification of the method for calculating the 95% confidence intervals, the exact definition of the analysis set that will be

used, and additional explorative analysis as well as information of the statistical software.
95 % confidence intervals will be reported for effect size measures Cohens d (comparison of difference in means) and correlation coefficients (correlation analysis).

Endpoints analysis

Primary endpoint analysis
Primary endpoint analysis: The statistical analysis is based on calculating a paired t-test regarding pain caused by PIVC rated by NRS with and without 10% lidocaine spray separately for the plantar side of the hand/vessel at the dorsum manus and the forearm/cubita.

Secondary endpoint analysis

1. A paired t-test regarding pain caused by PIVC rated by NRS in the dominant vs. non-dominant arm, separately analyzed for placebo/LDA and hand/forearm. 95% confidence interval will be reported for the effect size measure Cohens d for this difference in means.
2. A paired t-test regarding pain caused by PIVC rated by NRS at the plantar side of the hand/vessel at the dorsum manus vs. at the forearm/cubita, separately analyzed for placebo/LDA. 95% confidence interval will be reported for the effect size measure Cohens d for this difference in means.
3. The sample Pearson correlation coefficient between pain caused by PIVC rated by NRS and the anticipated pain rated by NRS, separately analyzed for placebo/LDA and hand/forearm as well as 95% confidence interval for correlation coefficient will be computed.
4. The sample Pearson correlation coefficient between pain caused by PIVC rated by NRS and the anticipated difficulty by the operator to insert the PIVC rated, separately analyzed for placebo/LDA and

hand/forearm as well as 95% confidence interval for the correlation coefficient will be computed.

5. Success rate of the venipuncture by descriptive analysis and chi-square test for comparing success rate between hand and forearm.
6. A t-test for independent samples comparing pain caused by PIVC rated by NRS between success and failure of insertion of PIVC. This analysis will be calculated separately for placebo/LDA and hand/forearm. 95% confidence interval will be reported for the effect size measure Cohens d for this difference in means.
7. The sample Pearson correlation coefficient between PCS Score (total sum score of 13 items ranging from 0-4) and pain caused by PIVC, separately analyzed for placebo/LDA and hand/forearm as well as 95% confidence interval for the correlation coefficient will be computed.

Interim analysis
No interim analysis with possible consequence of stopping the trial for futility or efficacy will be performed.

Software program(s)
All statistical analysis were performed with the help of IBM SPSS Statistics Version 23.

10. Documentation and data management

Documentation of study results

A subject screening and enrollment Log will be completed for all eligible or non-eligible subjects with the reasons for exclusion.

Case report form (CRF)
For each subject enrolled, a CRF will be completed and signed by the Investigator or a designated sub-Investigator. This also applies to those subjects who fail to complete the study. If a subject withdraws from the study, the reason will be noted in the CRF. Case report forms are to be

completed on an ongoing basis. CRF entries and corrections will only be performed by study site staff, authorized by the Investigator. The entries will be checked by trained personnel and any errors or inconsistencies will be checked immediately.

Data Collection

Data collected at all visits are entered into a CRF. The CRFs will be source documents verified following guidelines established before study onset. All data that is collected in the course of study visits (screening, treatment,), will be entered into a CRF.

Safekeeping

The investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents will be classified into two different categories: investigator's file with all essential study documents, and subject clinical source documents.

The investigator's file will contain the study protocol/amendments, CRFs, data clarification and query forms, EC/IRB and Regulatory Authority approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, screening and enrollment logs, and other appropriate documents/correspondence as per European Standard of EN ISO 14155 and regulatory requirements.

Subject clinical source documents include, but are not limited to subject hospital/clinic records, physician’s notes, appointment book, original laboratory reports, pathology and special assessment reports, consultant letters, etc.

These two categories of documents must be kept on file by the investigator for as long as needed to comply with national regulations. If source documents are not durable as long as needed (e.g. ECG printouts)

they must be preserved as a copy. No study document should be destroyed without prior written approval from the sponsor of the study. When source documents are required for the continued care of the subject, appropriate copies should be made for storing outside of the site.

All patient data will be pseudonymised with an identification number when entered into the eCRF and are only assignable to specific individuals with a number code. Only the study investigator of the particular center or authorized persons are able to make a connection between the number code and the individual patient.

Quality Control and Quality Assurance

Monitoring

No formal monitoring will be performed by an external monitoring company. The files and the conduct of the study will be internally checked by GCP experienced scientific personel not directly involved in the study. It will be the responsibility of the monitoring personel to inspect the CRFs at regular intervals throughout the study, to verify the adherence to the study protocol and the completeness, consistency and accuracy of the data being entered on them. The monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs/SADEs and the recording of the main outcome measures.

Audits and Inspections

Upon request, the investigator will make all study-related source data and records available to a qualified quality assurance auditor mandated by the sponsor or to regulatory authority inspectors. The main purpose of an audit or inspection is to confirm that the rights and welfare of the subjects have been adequately protected, and that all data relevant for assessment of safety and efficacy of the investigational product have appropriately been reported to the sponsor.

The study investigator Prim. Univ.-Prof. Dr. Lukas Hefler, MBA has access to all study data and statistics at any time.

Reporting and Publication

Final report

Within one year after the final completion of the study, a full Final Report will be written by the principal investigator. The Investigators will be asked to review and sign the Final Report.

Publication of study results

The findings of this study will be published by the sponsor (investigators) in a scientific journal and presented at scientific meetings. The manuscript will be circulated to all co-investigators before submission. Confidentiality of subjects in reports/publications will be guaranteed.

11. Ethical and legal aspects

Informed consent of subjects

Following comprehensive instruction regarding the nature, significance, impact and risks of this clinical investigation, the patient must give written consent to participation in the study. During the instruction the patients are to be made aware of the fact that they can with-draw their consent – without giving reasons – at any time without their further medical care being influenced in any way.

In addition to the comprehensive instructions given to the patients by the investigator, the patients also receive a written patient information sheet in comprehensible language, explaining the nature and purpose of the study and its progress. The patients must agree to the possibility of study-related data being passed on to relevant authorities.

The patients must be informed in detail of their obligations in relation to the proband insurance in order not to jeopardize insurance cover.

Acknowledgement / approval of the clinical investigation

The investigator will submit this study protocol and any related document provided to the subject (such as subject information used to obtain informed consent) to an Ethics Committee (EC) or Institutional Review Board (IRB). Approval from the committee must be obtained before starting the clinical investigation, and should be documented in a dated letter to the investigator.

The clinical investigation shall be performed in full compliance with the valid legal regulations of the Republic of Austria.

The study must be notified to the Austrian Agency for Health and Food Safety (AGES) and Ethics Committee.

Changes in the Conduct of the Clinical Investigation Plan

Amendments of the clinical investigation plan

Proposed amendments must be submitted to the ECs. Substantial amendments may be implemented only after EC approval has been obtained. Amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented prior to receiving EC approval. However, in this case, approval must be obtained as soon as possible after implementation.

Termination of the clinical investigation

If the sponsor or the investigator decides to terminate the clinical investigation before it is completed, they will notify each other in writing stating the reasons of early termination. In terminating the study, the sponsor and the investigator will ensure the adequate consideration is given to the protection of the subject interests. The investigator or sponsor will notify the relevant regulatory authorities and EC. Documentation will be filled in the Trial Master (Clinical Investigation) clinical investigation and Investigator Files.

Insurance

During their participation in the clinical investigation the patients will be insured as defined by legal requirements. The investigator of the clinical investigation will receive a copy of the insurance conditions of the 'patients insurance'. The sponsor is providing insurance in order to indemnify (legal and financial coverage) the investigator/center against claims arising from the clinical investigation, except for claims that arise from malpractice and/or negligence. The compensation of the subject in the event of clinical investigation-related injuries will comply with the applicable regulations. Details on the existing patients insurance are given in the patient information sheet.

Confidentiality

The information contained in this document, especially unpublished data, is the property of the sponsor. It is therefore provided to you in confidence as an investigator, potential investigator, or consultant, for review by you, your staff, and an Ethics Committee or Institutional Review Board. It is understood that this information will not be disclosed to others without written authorization from the sponsor, except to the extent necessary to obtain informed consent from those persons to whom the medical device may be treated with.

Ethics and legal requirements

Declaration of Helsinki

The investigator will ensure that this study is conducted in full conformance with the principles of the "Declaration of Helsinki" (as amended at the 56th WMA General Assembly, Tokyo, Japan, 2008).

ICH: E6 (R2): Guideline for good clinical practice

This document addresses the good clinical practice, an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects.

It specifies general requirements intended to:

- protect the rights, safety and well-being of human subjects,
- ensure the scientific conduct of the clinical investigation and the credibility of the clinical
- investigation results,
- assist sponsors, monitors, investigators, ethics committees, regulatory authorities and other
- bodies involved in the conformity assessment of medical devices.

The investigator of the clinical investigation shall guarantee that only appropriately trained personnel will be involved in this. All clinical investigations must follow the European Standard of ICH E6 (R2) and the regulatory requirements.

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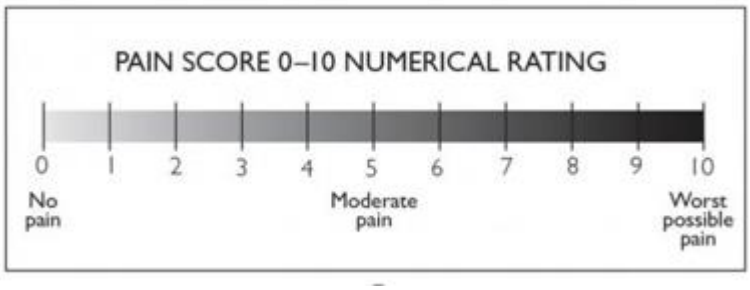
13. Appendix

13.1 Appendix 1 - Numeric Pain Rating Scale

The NRPS is a segmented numeric version of the visual analog scale in which a respondent selects a whole number (0-10 integers) that best reflects the intensity of his/her pain.

- The common format is a horizontal bar or line
- Similar to the VAS, the NPRS is anchored by terms describing pain severity extremes.

The 11-point numeric scale ranges from ‚0' representing one pain extreme (e.g."no pain") to ‚10' representing the other pain extreme (e.g. „pain as bad as you can imagine" or „worst pain imaginable")



14.2 Appendix 2 - Pain Catastrophizing Scale

Pain Catastrophizing Scale (Copyright 1995, 2001, 2004, 2006, 2009 Michael JL Sullivan, PhD)
Everyone experiences painful situations at some point in their lives. Such experiences may include headaches, tooth pain, joint or muscle pain. People are often exposed to situations that may cause pain such as illness, injury, dental procedures or surgery.

We are interested in the types of thoughts and feeling that you have when you are in pain. Listed below are thirteen statements describing different thoughts and feelings that may be associated with pain. Using the scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain.

	Not at all	To a slight degree	To a moderate degree	To a great degree	All the time
I worry all the time about whether the pain will end	0	1	2	3	4
I feel I can't go on	0	1	2	3	4
It's terrible and I think it's never going to get any better	0	1	2	3	4
It's awful and I feel that it overwhelms me	0	1	2	3	4
I feel I can't stand it anymore	0	1	2	3	4
I become afraid that the pain will get worse	0	1	2	3	4
I keep thinking of other painful events	0	1	2	3	4
I anxiously want the pain to go away	0	1	2	3	4
I can't seem to keep it out of my mind	0	1	2	3	4
I keep thinking about how much it hurts	0	1	2	3	4
I keep thinking about how badly I want the pain to stop	0	1	2	3	4
There's nothing I can do to reduce the intensity of the pain	0	1	2	3	4
I wonder whether something serious may happen	0	1	2	3	4

DECLARATION OF SPONSOR

VENLID: A prospective, randomized, double-blind, controlled trial on the application of a 10%-lidocaine spray prior to the insertion of a peripheral intra-venous catheter in female adults

I have read this trial protocol and agree that it contains all the information required to conduct the trial. I agree to conduct the trial as set out in this protocol. In particular, I agree to adhere to the moral, ethical and scientific principles governing clinical research as set out in the current version of the Declaration of Helsinki, the ICH Guideline on Good Clinical Practice E6 (R2) and the appropriate national laws and regulations.

I agree to handle all information concerning the trial confidentially.

_____	_____
Place, Date	Printed Name
_____	_____
Address	Signature