Prospective, Crossover, Open Label Study to Evaluate the Effects of Vibration Anesthesia with DigiVibe on Pain in Subjects Undergoing Intramuscular Injections, Subcutaneous Injections, and Fingersticks (VIB-DIGI)

Short Title: Effects of DigiVibe on Pain in Subjects Undergoing Intramuscular Injections, Subcutaneous Injections, and Fingersticks (VIB-DIGI)

Protocol Date: May 4, 2025

Version #: 1.0

ABBREVIATIONS USED IN THE PROTOCOL

Abbreviation	Term
AE	Adverse Event
SAE	Serious Adverse Event
GCP	Good Clinical Practice
IRB	Institutional Review Board
ICF	Informed Consent Form
HIPAA	Health Insurance Portability and Accountability Act of 1996
EOS	End of Study
FDA	Food and Drug Administration
US	United States
EMR	Electronic Medical Record
SOA	Schedule of Activities
SAS	Statistical Analysis System
IM	Intramuscular
SC	Subcutaneous
TENS	Transcutaneous Electrical Nerve Stimulation
LB	Long Buccal
IAN	Inferior Alveolar Nerve
FAS	Facial Anxiety Scales
VAS	Visual Analog Scale
SSI	Symptom Severity Index
H_0	Null Hypothesis
H_A	Alternative Hypothesis
n=	Number
NS	Normal Saline
BMI	Body Mass Index
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
BP	Blood Pressure

Table of Contents

1 INTRODUCTION

1.1 Background and Significance

Each year in the United States, millions of individuals undergo medical procedures involving needles, including intramuscular (IM) injections, subcutaneous (SC) injections, and fingersticks for blood glucose monitoring and other point of care testing. These procedures are essential for administering vaccines, managing chronic conditions, and monitoring health. However, a significant portion of the population experience a fear of needles due to the associated pain, which can impact their willingness to undergo these necessary medical interventions. This fear can result in missed vaccinations, poor adherence to medication regimens, and inadequate monitoring of conditions, such as diabetes. Understanding the prevalence and impact of needle fear due to pain is crucial for developing strategies to improve patient compliance and overall health outcomes.

Pain is transmitted through nociceptors, derived from neural crest cells in the spinal cord during gestation and relayed by the thalamus. While the full mechanism of pain is unclear, the 'Gate Control Theory of Pain', introduced by Melzack and Wall in the 1960s, in widely used. This Theory suggests that open spinal gates allow for painful stimuli to permeate through the body while closed gates halt that process [1]. This theory also highlights two types of afferent fibers that mediate the pain stimuli – fast-transmitting myelinated A fibers (pricking pain) and slow-transmitting unmyelinated C fibers (burning pain) [1].

Pain associated with needle-based procedures can be reduced through a variety of non-interventional methods, including distraction techniques, cooling, and tactile stimulation. One such method gaining attention is vibration therapy (also known as vibration anesthesia), which uses localized mechanical stimulation to interfere with pain signal transmission and reduce perceived discomfort. Vibrations serve as a competing sensory input that can help block pain signals from reaching the brain, consistent with the gate control theory of pain (eg. closed gate process). Over the years, vibration devices such as the Transcutaneous Electrical Nerve Stimulation (TENS) Unit machine (1974), Buzzy (2009), and Vibracool (2015), have demonstrated that non-painful stimuli effectively be used to reduce the perception of pain.

DigiVibe is a cordless, handheld device designed to reduce the pain caused by needles that is a U.S. Food and Drug Administration (FDA) registered device to be used to reduce

the pain associated with fingerstick blood glucose testing. By applying targeted vibrations to the skin prior to a needle stick, it interferes with pain signal transmission to the brain, making the process more comfortable for users.

A prospective, randomized study comparing vapocoolant (cold) spray versus vibration anesthesia evaluated pre-injection (expected pain) and a post-injection pain (actual perceived pain). One-hundred and eighty (180) subjects with arthritis, tendinopathy, or compression neuropathy of the hand, wrist, or elbow were randomized to one of three groups – no anesthesia (n=60), injection with vapocoolant spray (n=60), and injection with vibratory anesthesia (n=60). Subjects were provided a 10-point Likert scale pre-injection, to assess expected pain, and a post-injection, to assess actual perceived pain.

Pre-injection pain scores for no anesthesia, vapocoolant, and vibration were 5.57, 5.32 (p-value 0.01470), and 5.73 (p-value 0.0446), respectively. Post-injection pain scores were the following for no anesthesia 5.18 (CI: -1.22 to 0.45), cold spray 4.12 (p-value: 0.1470; CI: -1.95 to 0.45), and vibration anesthesia 4.18 (p value 0.0446; CI: -2.34 to 0.76). These results suggest that vibration anesthesia could be a useful adjunct for injections of the hand, wrist, or elbow – which has been consistent with previously published data [3].

The Vibration Device to Control Injection Discomfort trial analyzed the discomfort level of 60 subjects (30 men and 30 women) who needed local anesthesia for intraoral long buccal (LB) and inferior alveolar nerve (IAN) injections. This study evaluated pain and anxiety levels during anesthesia administration with the DentalVibe® Injection Comfort System, which uses pulsation to reduce discomfort during injection administration. Anxiety prior to an injection was measured using the facial anxiety scales (FAS), acute pain intensity during injection was assessed with the Visual Analog Scale (VAS), and symptom history over the past six months was recorded using the Symptom Severity Index (SSI) [4]. The study did not showcase statistically significant differences in any measures. However, individuals who did not receive DentalVibe® had higher scores across all measures for both injections indicating that there was a clinically meaningful reduction in pain with the use of DentalVibe® in combination with injections during dental anesthesia[4].

1.2 Risk Assessment

DigiVibe

The DigiVibe device is considered to be safe and noninvasive and the potential risks to subjects in this study are minimal, if any.

Skin Irritation or Discomfort

Prolonged or overly intense use of DigiVibe in one area of the skin could cause temporary redness, bruising, or minor soreness, specifically in patients with sensitive skin.

Normal Saline and Injections

Normal saline will be used for intramuscular and subcutaneous injections and, while it is an inert and widely used solution, intramuscular and subcutaneous injections may have some potential risks, if any.

As with any standard of care injections, subjects may experience soreness, pain, redness, swelling, or tenderness at the injection site. Mild bruising or local irritation may also occur with a potential for minor bleeding at the injection site. Though rare, there is a small risk of skin or soft tissue infection at the injection site.

2 ETHICS

2.1 Good Clinical Practice (GCP)

This study will be conducted in accordance with Good Clinical Practice (GCP), in accordance with the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50). The study will be conducted in compliance with the protocol.

All potential protocol deviations or violations must be reported to the IRB immediately. A protocol deviation or violation is defined as a violation of the GCP guidelines regarding the study protocol, which is likely to significantly affect the safety of the subjects in the

study or the scientific validity of the study. Study staff involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks and this study will not use study staff where there has been scientific misconduct or fraud (e.g., loss of medical licensure, debarment).

2.2 Institutional Review Board (IRB)

Before initiation of the study, the investigator must have received IRB approval for the protocol, Informed Consent Form (ICF), subject recruitment materials (e.g., advertisements), and any other written information to be provided to subjects.

During the clinical study, any amendment to the clinical trial protocol must be submitted to the IRB before implementation, unless the change is necessary to eliminate an immediate hazard to the subjects, in which case the IRB should be promptly informed. The IRB should also be informed of any event likely to impact the safety of subjects in the clinical trial. The investigator must send a progress report to the IRB at least annually, as well as a summary of the clinical trial's outcomes at the end of the clinical trial.

2.3 Informed Consent

The investigator will ensure that the ICF includes all elements required by GCP and applicable regulatory requirements, as well as follow the ethical principles within the Declaration of Helsinki. The investigator will ensure that the ICF is reviewed and approved by the IRB prior to use in a clinical trial.

The Investigator, or a person designated by the Investigator, should fully inform the subject of all pertinent aspects of the clinical trial including the purpose, potential risks, required procedures, etc. in which they volunteer to participate. All subjects should be informed about the study in a language and at a level they are able to understand. In circumstances where consent cannot be given to subjects, their legally acceptable representatives must be clearly and fully informed about the purpose, potential risks, required procedures, etc. regarding the clinical trial in which the subject will participate.

Prior to a subject's participation in the clinical trial, the written ICF should be signed and dated personally (by the subject) or by the subject's legally acceptable representative and by the person who conducted the informed consent discussion. A copy of the signed and dated written ICF will be provided to the subject.

3 HYPOTHESIS

Null Hypothesis (H_0): DigiVibe vibration anesthesia has no clinically significant impact on pain scores.
Alternative Hypothesis (H_A): DigiVibe vibration anesthesia has a clinically significant impact on pain scores.

4 STUDY DESIGN

4.1 Description

This is a single-center, unblinded, prospective, cross-over study. The study population will include twenty (n=20) healthy subjects (10 men and 10 women) over the age of 18 with a self-reported fear/dislike of needles. Subjects who qualify for the study based on the study inclusion and exclusion criteria and who consent to participate in the study will undergo two (2) intramuscular (IM) injections in the deltoid muscle, two (2) subcutaneous (SC) injections in the abdomen, and two (2) fingersticks with a lancing device in the middle finger. Normal Saline (NS) will be used for the IM and SC injections. The study duration per subject is expected to be one (1) day.

While the complete mechanisms of pain and pain diversion are not completely understood, DigiVibe locally targets the skin's pain receptors. Therefore, it is proposed that the vibrations from the DigiVibe device will counteract and/or lessen the pain around the injection site. This study will determine whether the use of DigiVibe during a procedure requiring injections provides greater reduction in pain than injections with no intervention (standard of care). This information will aid healthcare providers in selecting the best approach to management of pain in patients who must undergo injections that could cause pain and may benefit from additional pain reduction.

4.2 Study Objectives / Endpoints

Objective	Endpoint
Primary	
To demonstrate if the use of DigiVibe is superior to no intervention in reducing pain scores during intramuscular injections, subcutaneous injections, and fingersticks.	Difference between DigiVibe and no intervention on pain scores.

4.3 Study Population

4.3.1 Study Subjects and Approximate Number of Subjects

This is a single-center study which will include the participation of twenty (20) subjects.

4.3.2 Eligibility Criteria

Inclusion Criteria:

Subjects must meet each of the following inclusion criteria to be eligible for enrollment into the study:

1. Age ≥ 18 years
2. BMI 18.5-29.9 kg/m^2 (normal)
3. Self-reported fear/dislike of needles

Exclusion Criteria:

Subjects presenting with any of the following exclusion criteria will not be eligible for enrollment into the study:

1. Chronic (daily) use of nonsteroidal anti-inflammatory drugs (NSAIDs) (i.e. ibuprofen, aspirin, naproxen, etc.), antiplatelet medications (i.e. clopidogrel, prasugrel, ticagrelor, cangrelor, cilostazol, etc), or anticoagulant medications (i.e. warfarin, dabigatran, rivaroxaban, apixaban, edoxaban, heparin, enoxaparin, fondaparinux, etc.)

- Note: NSAIDs used as needed are not excluded as long as they are not used within 3 days of study screening and enrollment

2. Chronic (daily) use of analgesics (i.e. acetaminophen, NSAIDs [ie. ibuprofen, naproxen], opioids [ie. morphine, oxycodone, fentanyl], lidocaine, cannabinoids [ie. CBD, THC],)
    - Note: analgesics used as needed are not excluded as long as they are not used within 3 days of study screening and enrollment
3. Any condition in the opinion of the study investigator that would potentially confound the results of this study

4.4 Study Duration

4.4.1 Approximate Duration of Subject Participation

Subjects will actively participate in the study for up to one (1) day.

Discontinuation will be based upon investigator's clinical determination and/or by subject decision. All subjects are free to terminate their participation in the study at any time, and the details regarding discontinuation will be recorded.

4.4.2 Screen Failures

If a subject consents to participate in the clinical trial and is not enrolled, they are considered a screen failure. A subject can screen fail at any time during Visit 1 prior to initiating study procedures. The reason for the subject screen failing must be documented in the subject's source documentation.

4.4.3 Premature Study Treatment Discontinuation

If a subject decides to discontinue their study participation at any time during Visit 1 and after study procedures (post consent) have begun, the reason(s) of study discontinuation must be recorded in the subject source documentation.

If the subject discontinued study participation due to an adverse event (AE), the AE must be reported, and the subject will be followed up after discontinuation until the AE is resolved or considered medically stable by the investigator.

4.4.4 Withdrawal documentation

The subject may withdraw consent at will at any time. The subject's request to withdraw from the trial must always be respected. In case of withdrawal, the investigator will record the reason for subjects' withdrawal.

Subject participation in the study may be discontinued for reasons including, but not limited to:

- Withdrawal of subject's consent
- Subject preference
- Decision of the subject's study investigator

4.4.5 Follow-up on Withdrawn Subjects

Early discontinuation does not nullify the need to follow AEs until resolution or stabilization.

4.4.6 Approximate Duration of Study

This study is anticipated to be completed within approximately one (1) month, including subject enrollment, data collection, and analysis.

4.5 Study Visits

<u>Pre-screening</u>

Potential subjects whose BMI is 18.5-29.9 kg/m² will be identified in the study investigator's clinic Electronic Medical Record (EMR) and contacted to determine if they have a fear/dislike of needles.

<u>Visit 1 (Day1); In-Person Onsite Visit)</u>

Subjects will be consented and assessed for eligibility to enroll in the study. Subject targeted concomitant medications and targeted medical history will be reviewed and recorded. The subjects BMI and vital signs will be obtained.

Following confirmation of eligibility, subjects will be enrolled. Subjects will first undergo two fingersticks with a 30-gauge Unistik lancing device on pulp of their middle finger. The first fingerstick will be performed with no intervention (as per standard of care).

Immediately following the fingerstick, subjects will be provided the VAS pain scale and asked to assess their level and pain and document it by circling the level of pain. After waiting 5 minutes, the DigiVibe device will be applied to the pulp of the other middle finger for 20 seconds, the lancet device will be inserted into the center of the DigiVIbe device, and then the second fingerstick will be immediately performed with the DigiVibe device still vibrating through the release of the lancing device. Immediately following the fingerstick, subjects will be provided the VAS pain scale and asked to assess their level and pain and document it by circling the level of pain.

Subjects will then undergo two SC injections with a 30-gauge 4mm needle on the lower quadrant of their abdomen at least 2 inches from the belly button. The first SC injection will be performed with no intervention (as per standard of care). Immediately following the injection, subjects will be provided with the VAS pain scale and asked to assess their level and pain and document it by circling the level of pain. After waiting 5 minutes, the DigiVibe device will be applied to the other side of the abdomen on the lower quadrant for 20 seconds and then the second SC injection will be immediately performed with the DigiVibe device still vibrating the injection site during the entire injection process. Immediately following the SC injection, subjects will be provided the VAS pain scale and asked to assess their level and pain and document it by circling the level of pain.

Subjects will then undergo two IM injections. Subjects will undergo alternating assignments to either a 25-gauge 1 inch needle or a 30-gauge 1 inch needle in the upper arm deltoid muscle. The alternating assignment should be performed separately for the males and females so there is an equal distribution of males and females assigned to 25-gauge and 30-gauge. The alternating assignments must be documented. The first IM injection will be performed with no intervention (as per standard of care). Immediately following the injection, subjects will be provided with the VAS pain scale and asked to assess their level and pain and document it by circling the level of pain. After waiting 5 minutes, the DigiVibe device will be applied to the other deltoid muscle for 20 seconds and then the second IM injection will be immediately performed with the DigiVibe device still vibrating the injection site during the entire injection process. Immediately following the IM injection, subjects

will be provided the VAS pain scale and asked to assess their level and pain and document it by circling the level of pain.

Subject AEs will be recorded.

4.6 Study Procedures

The following procedures will be performed at the times shown in the Study Treatments Investigational Medical Products

- Test Product: DigiVibe Vibrating Anesthetic Device
- Non-Intervention: Standard of Care

4.6.1.1 **Packaging, Labeling, and Storage**

The DigiVibe, Normal Saline, and injection/lancing supplies will be obtained from commercial batches and stored in their original packaging without adjustments or modifications to the labeling. The investigational product (DigiVibe) will not be masked.

Study Schedule of Activities (SOA):

Demography

Demography will be recorded at Visit 1 and will consists of date of birth, sex, ethnicity, and race.

Targeted Concomitant Medications

Targeted concomitant medications will be reviewed and recorded at Visit 1. A targeted concomitant medication is any NSAID, antiplatelet, anticoagulant, or analgesic treatment that the subject received within one (1) month of screening and enrollment into the study. All targeted concomitant medications should be documented in the subject's source documents.

Targeted Medical History

Targeted medical history will be reviewed and recorded at Visit 1. Targeted medical history includes medical events associated with the use of NSAIDs, antiplatelets, anticoagulants, and analgesics.

Vital Signs (height, weight, & blood pressure)

Subjects will have their height, weight, and blood pressure obtained using calibrated, digital devices. Vital signs will be documented in the subject's source documents.

Fingersticks and Injections (Without Intervention/DigiVibe)

Subjects will first undergo a fingerstick with a 30-gauge Unistik lancing device on their middle finger with no intervention (as per standard of care). For the fingerstick, the targeted area of the middle finger will be disinfected with alcohol, the lancing device will be pressed firmly against the pulp of the middle finger, and the lancet will be activated.

Subjects will then undergo a SC injection with a 30-gauge 4mm needle on the lower quadrant of their abdomen at least 2 inches from the belly button with no intervention (as per standard of care). For the SC injection, 0.5 mL of NS will be drawn into the syringe, the needle will be replaced with a new 30-gauge 4mm needle, the targeted area of the lower abdomen will be disinfected with alcohol, the needle will be inserted at a 90-degree angle, the NS will be injected slowly but steadily, and the needle will be withdrawn quickly.

Subjects will then undergo an IM injection with either a 25-gauge 1 inch needle or a 30-gauge 1 inch needle in upper arm deltoid muscle with no intervention (as per standard of care). For the IM injection, 0.5 mL of NS will be drawn into the syringe, the needle will be replaced with a new 25-gauge 1 inch needle or 30-gauge 1 inch needle (depending on the subject's assignment (see above), the targeted area of the upper arm deltoid muscle will be disinfected with alcohol, the needle will be inserted at a 90-degree angle, the NS will be injected slowly but steadily, and the needle will be withdrawn quickly.

Fingersticks and Injections (With DigiVibe)

Subjects will undergo a fingerstick with a 30-gauge Unistik lancing device on their middle finger using the DigiVibe device. For the fingerstick, the targeted area of the middle finger will be disinfected with alcohol, the DigiVibe device will be applied to the pulp of the middle finger for 20 seconds, the lancet device will be inserted into the center of the DigiVIbe device, and then the second fingerstick will be immediately performed with the DigiVibe device still vibrating through the release of the lancing device.

Subjects will then undergo a SC injection with a 30-gauge 4mm needle on the lower quadrant of their abdomen at least 2 inches from the belly button using DigiVibe device. For the SC injection, 0.5 mL of NS will be drawn into the syringe, the needle will be replaced with a new 30-gauge 4mm needle, the targeted area of the lower abdomen will be disinfected with alcohol, the DigiVibe device will be applied to the abdomen on the lower quadrant for 20 seconds, the needle will be inserted at a 90-degree angle through the center of the DigiVibe device (with the DigiVibe device still vibrating), the NS will be injected slowly but steadily, and the needle will be withdrawn quickly. The DigiVibe device should continue vibrating on the injection site during the entire injection process until the needle is removed.

Subjects will then undergo an IM injection with either a 25-gauge or 30-gauge 1 inch needle (depending on their previous assignment) in the upper arm deltoid muscle using the DigiVibe device. For the IM injection, 0.5 mL of NS will be drawn into the syringe, the needle will be replaced with a new 25-gauge or 30-gauge (depending on their assignment) 1 inch needle, the targeted area of the upper arm deltoid muscle will be disinfected with alcohol, the DigiVibe device will be applied to the deltoid muscle for 20 seconds, the needle will be inserted at a 90-degree angle through the center of the DigiVibe device (with the DigiVibe device still vibrating), the NS will be injected slowly but steadily, and the needle will be withdrawn quickly. The DigiVibe device should continue vibrating on the injection site during the entire injection process until the needle is removed.

<u>Visual Analog Scale (VAS)</u>

Subjects will be provided with a paper copy of the VAS, a validated scale that allows subjects to measure their pain on a visual horizontal grading scale of zero (0) to ten (10).

Subjects will use the VAS to provide their subjective measure of their pain level immediately following each fingerstick and injection for a total of six (6) completed scales.

Review AEs

AEs will be collected during the visit, which includes any new clinically significant sign or symptom or any clinically significant worsening of a pre-existing sign or symptom. The definitions of AEs and serious AEs (SAEs) are provided below.

Study Exit

After the procedures in the visit are complete, the subject is exited from the study.

4.7 Study Treatments

4.7.1 Investigational Medical Products

- Test Product: DigiVibe Vibrating Anesthetic Device
- Non-Intervention: Standard of Care

4.7.1.1 Packaging, Labeling, and Storage

The DigiVibe, Normal Saline, and injection/lancing supplies will be obtained from commercial batches and stored in their original packaging without adjustments or modifications to the labeling. The investigational product (DigiVibe) will not be masked.

4.8 Study Schedule of Activities (SOA)

Procedure	Screening/ Enrollment Visit 1/ Day 1
	In-Person
Informed Consent	X
Inclusion/Exclusion criteria	X
Demographics	X
Vital Signs (height, weight, & BP)	X
Targeted Medical History	X

Targeted Concomitant Medications	X
Fingerstick **without** DigiVibe	X
Subject VAS Pain Scale (post fingerstick **without** DigiVibe)	X
Subcutaneous Injection **without** DigiVibe	X
Subject VAS Pain Scale (post subcutaneous injection **without** DigiVibe)	X
Intramuscular Injection **without** DigiVibe	X
Subject VAS Pain Scale (post intramuscular injection **without** DigiVibe)	X
Fingerstick **with** DigiVibe	X
Subject VAS Pain Scale (post fingerstick **with** DigiVibe)	X
Subcutaneous Injection **with** DigiVibe	X
Subject VAS Pain Scale (post subcutaneous injection **with** DigiVibe)	X
Intramuscular Injection **with** DigiVibe	X
Subject VAS Pain Scale (post intramuscular injection **with** DigiVibe)	X
Adverse events	X
Study Exit	X
Data Entry	X

4.9 Data Analysis

4.9.1 Statistical Analysis Plan

Demographics and baseline characteristics of study subjects will be summarized, as will VAS pain scores for the intervention (DigiVibe) and standard care. The primary analysis will be a paired t-test or Wilcoxon signed-rank test (depending on normality of VAS scores) to compare pain scores between standard care and DigiVibe. These tests will be performed individually for each of the injection sites (fingerstick, SC, IM).

4.9.2 Statistical Power and Sample Size Considerations

For any of the three (3) injection sites individually, a sample size of 20 patients achieves ≥80% power to detect a mean of paired differences of 1.0 with an estimated standard deviation of differences of 1.5 and with a significance level (α) of 0.05 using a two-sided paired t-test. A smaller difference (e.g., 0.75) would be detectable with power ≥88% at an α=0.05 using the same test, if the standard deviation is 1.0.

4.10 Data Management

4.10.1 Data Collection and Storage

Data required by the protocol will be collected using a data collection form created by the investigative site. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the data collection form. Excel worksheets will be used to create the data repository for the analysis data set which will be de-identified and employ range checking derived from the study data dictionary. Final data merges for analysis will be performed with statistical analysis system (SAS) software. Electronic data will be stored on encrypted drives and backed up routinely to a secure server. At the End of Study completion, all electronic data will be stored on a password protected universal serial bus (USB) flash drive and archived with study documents.

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). All physical records will be kept in a locked file cabinet.

4.10.2 Records Retention

The investigator must agree to archive the study documentation (both electronic and paper-based records) in an archive after completion or discontinuation of the trial. The investigator should not destroy any documents without prior permission from Suthe Dermal. If the investigator cannot archive the documents at the trial site, they should notify Suthe Dermal. At the conclusion of this study, data from this study will be archived for 2 years for possible use in future research studies.

5 SAFETY MONITORING

5.1 Adverse Event Reporting

Clinical AEs and SAEs will be monitored from signing of the ICF until completion of all study procedures are completed. All AEs and SAEs will be reported to an Investigator regardless of whether they are considered study-related. The date and time of onset and outcome, seriousness, intensity, action taken, and causality to study treatment will be assessed by a study investigator.

5.2 Definitions

An **adverse event** (AE) is any untoward, undesired, or unplanned event in the form of signs, symptoms, disease, or laboratory or physiological observations occurring in a person given a test article or in a clinical study. This includes a clinically significant worsening of a concomitant illness and clinical laboratory abnormalities which are clinically significant, i.e. an abnormality that suggests a disease and is of a severity that requires active management. The event does not need to be causally related to the device or clinical study.

The following definitions are used when assessing the intensity of an AE:

- Mild: no or transient symptoms, no interference with the subject's daily activities.
- Moderate: marked symptoms, moderate interference with the subject's daily activities.
- Severe: considerable interference with the subject's daily activities; unacceptable.

The following definitions are used when assessing the causality (relationship) of an AE:

- Related: A causal relationship between the study treatment and the AE is a reasonable possibility. The Investigator must further qualify the degree of certainty as "possible" or "probable."

- Possible: A causal relationship is conceivable and cannot be dismissed.
- Probable: Good reason and sufficient documentation to assume a causal relationship.
- Not Related: A causal relationship between the study treatment and the AE is not a reasonable possibility.

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment;
- The course of the event, considering especially the effect of the discontinuation of study treatment or the reintroduction of study treatment, as applicable;
- Whether the event is known to be associated with the study treatment or with other similar treatments;
- The presence of risk factors in the study subject known to increase the occurrence of the event; and,
- The presence of non-study treatment-related factors that are known to be associated with the occurrence of the event.

The following definitions are used when assessing the outcome of an AE:

- Recovered/resolved: The subject has fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial-related activity after the subject signed the ICF.
- Recovering/resolving: The condition is improving, and the subject is expected to recover from the event. This term is only applicable if the subject has completed the trial or has died from another AE.
- Recovered/resolved with sequelae: The subject has recovered from the condition, but with lasting effect due to a disease, injury, treatment or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE.
- Not recovered/not resolved: The condition of the subject has not improved, and

the symptoms are unchanged, or the outcome is not known.

- Unknown: This term is only applicable if the subject is lost to follow-up.

SAEs are any untoward medical occurrence affecting the pain site:

- Results in death;
- Is life-threatening (i.e., the subject was at immediate risk of death from the AE as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect;
- Is a medically important event.

5.3 Recording and Reporting

A subject's AEs and SAEs will be recorded and reported from the signing of the informed consent form until the subject's final study procedures are completed. All SAEs must be reported to the PI.

6 ADMINISTRATIVE PROCEDURES

6.1.1 Changes to the Protocol

There are to be no changes to the protocol without written approval from the Investigators and sponsors. Protocols will be followed as written.

Any change to the protocol requires a written protocol amendment or administrative change that must be approved before implementation by the sponsor and IRB. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require additional approval by the applicable IRBs of all investigational sites. These requirements should in no way prevent any immediate action from being taken by the Investigator or by the Sponsor in the interest of preserving the safety of all subjects included in the study. If an immediate change to the protocol is felt by the Investigator to be necessary for safety reasons, the sponsor and

IRB must be notified promptly.

Changes affecting only the administrative aspects of the study do not require formal protocol amendments or IRB approval, but the IRB must be kept informed of such changes. In these cases, the Principal Investigator will send a letter to the IRB detailing such changes.

6.1.2 Adherence to the Protocol

The Investigators will conduct the study in strict accordance with the protocol, which has been written to enable the Investigator's compliance with Good Clinical Practices.

6.1.3 Monitoring Procedures

6.1.3.1 Responsibilities of the Principal Investigator

The principal investigator is required to ensure compliance with all procedures required by the clinical trial protocol and agrees to provide reliable data requested by the clinical trial protocol in an accurate and legible manner. The principal investigator may delegate other individuals as they deem appropriate as sub-investigators to assist in the conduct of the clinical trial. The sub-investigators will work under the responsibility of the principal investigator. The principal investigator will provide them with a copy of the clinical trial protocol and all necessary information.

6.1.3.2 Responsibilities of the Monitor

The monitor of this clinical trial is responsible for taking all reasonable steps to ensure the proper conduct of the clinical trial regarding ethics, protocol compliance, and integrity and validity of the data recorded. Thus, the main duty of the monitor is to help the principal investigator maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the clinical trial.

Throughout the clinical trial, the monitor will contact the site through monitoring visits or phone calls to review study progress, investigator and patient compliance with the protocol, and any study-related issues. The monitoring visits will include, but not be limited to, review of the following aspects: patient ICFs, patient recruitment and follow-up, SAE

documentation and reporting, AE documentation, compliance with the study protocol, and quality of data. The monitor must check the data collected against the source documents.

7 PUBLICATION PLAN

Results from this research (without any subject identifiers) may be submitted for journal publication or presentation at national meetings. Important findings may be submitted to conferences and for publication in peer-reviewed scientific journals. The identity of the subjects may not be disclosed, unless required by law, to any persons not immediately involved in the study or the study procedures.

8 REFERENCES

1. Campbell TS, Johnson JA, Zernicke KA. Gate Control Theory of Pain. In: Encyclopedia of Behavioral Medicine. Cham: Springer International Publishing; 2020.

2. Smith K, Comite S, Balasubramanian S, Carver A, Liu J. Vibration Anesthesia: A Noninvasive Method of Reducing Discomfort Prior to Dermatologic Procedures. Dermatology Online Journal. 2004.

3. Weeks D, Faillace J. Vibratory Anesthesia's effect on pain perception in upper extremity corticosteroid injections. US National Library of Medicine. July 2022.

4. Shaefer JR, Lee SJ, Anderson NK. A Vibration Device to Control Injection Discomfort. Compend Contin Educ Dent. 2017 Jun;38(6):e5-e8. PMID: 28586233.