***iNSERT tITLE OF THE PROTOCOL***

*[Include* ***design*** *(e.g. randomized, double blind, placebo controlled, etc), if the study* ***is multi-center****, the* ***investigational device****, and* ***target disease(s****)]*

|  |  |
| --- | --- |
| **Regulatory Sponsor:** | *Insert the Name of the Sponsor-Investigator*  *Insert Institution*  *Insert Address*  *Insert Phone Number* |
| **Funding Sponsor:** | *Myoscience, Inc.*  *1600 Seaport Blvd.*  *Ste. 450*  *Redwood City, CA 94063* |
| **Study Product:** | *iovera°-Investigator* |
| **Protocol Number:** | *Insert Protocol Number Used by Sponsor* |

**Initial version:** [date]

**Amended:** [date]

**Amended:** [date]

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**List of Abbreviations**

# Study Summary

|  |  |
| --- | --- |
| Title | *Full title of protocol* |
| Short Title | *Shortened title, if one is typically used by you or your institution* |
| Protocol Number | *The standard protocol number used to identify this study.* |
| Methodology | *Design attributes such as single blind, double blind or open label; Randomized, placebo or active placebo control; cross-over design, etc.* |
| Study Duration | *Estimated duration for the main protocol (e.g. from start of screening to last subject processed and finishing the study)* |
| Study Center(s) | *Single-center or multi-center. If multi-center, note number of projected centers to be involved.* |
| Objectives | *Brief statement of primary study objectives* |
| Number of Subjects | *Number of subjects projected for the entire study (e.g. not for simply one site, rather for entire study, all sites combined)* |
| Diagnosis and Main Inclusion Criteria | *Note the main clinical disease state under study and the key inclusion criteria (i.e. not the entire list that will appear later in the protocol –rather only the key inclusion criteria)* |
| Study Product, Dose, Route, Regimen | *Study device name (generic name, though can also state marketed name if name-brand used in the study).* |
| Duration of administration | *Total duration of product administration (including any open-label lead-in, if applicable).* |
| Reference therapy | *Note if there is a standard reference therapy against which the study product is being compared, or if the reference is a placebo* |
| Statistical Methodology | *A very brief description of the main elements of the statistical methodology to be used in the study. (As few lines as possible).* |

# Introduction

*The introduction should open with remarks that state that this document is a clinical research protocol and the described study will be conducted in compliance with the protocol, Good Clinical Practices standards and associated Federal regulations, and all applicable research requirements. The rest of the introduction is broken out into subsections. Example language for the first paragraph under “Introduction” and before the section “1.1 Background”:*

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

## Background

*This section should contain a background discussion of the target disease state to which the investigational product(s) hold promise, and any pathophysiology relevant to potential study treatment action.*

## Device Description

*This section should contain a description of the investigational product.*

The myoscience iovera° device is a next generation device designed to temporarily reduce pain. The device consists of a reusable, portable Handpiece, along with single-patient use Smart Tips (aka cryoprobes) and disposable nitrous oxide (N2O) cartridges. The Smart Tip contains embedded software that manages procedure parameters and provides physician feedback throughout all states of device preparation, treatment and post-treatment via communication with the Handpiece. The Handpiece is battery powered and is stored and recharged via the Charging Dock.

The iovera° device produces the desired effect through initiation of a cooling cycle. Each cooling cycle is initiated by insertion of the Smart Tip into the selected procedure site and activation of the cryogen flow. A freezing zone forms around the end of the Smart tip affecting the adjacent tissue.

The cryogen is provided in a nitrous oxide cylinder attached to a custom filter, known as the Cartridge. To remove contaminants that may be present in the cylinder, a custom filter is added to the cylinder to filter the liquid nitrous oxide before it enters the Handpiece. This ensures optimal performance of the device.

A specially designed Smart Tip is included. The Smart Tip needles are made of stainless steel and have a closed-tip, fully enclosing the cryogen. As the cryogen gas travels through the length of the needle, an ice ball develops around the needle causing the surrounding tissue to be frozen. Operation instructions and further details on the device are provided in the ***User Guide***.

## Regulatory Status

The iovera° device is 510(k)-cleared (K133453) for producing lesions in peripheral nervous tissue by application of cold to selected sites for blocking pain. Cleared indications include general tissue destruction during surgical procedures and cryotreatment of nerves to block pain.

In studies of pain and facial wrinkle reduction, myoscience and an independent review board have determined that the iovera° device is a non-significant risk device under 21 CFR §812.2(b) as described for use within prior protocols. Therefore, an approved Investigational Device Exemption (IDE) from FDA was not required to legally perform these studies in the US.

Additionally, as defined in the FDA definition of significant and non-significant risk devices per 21 CFR 812.2(b) and 812.2(m) the iovera° device is NOT:

* + An implant; or
  + Used in supporting or sustatining human life; or
  + Substantially important in diagnosing, curing, mitigating or treating disease or preventing impaiment of human health.

*This section should contain the rationale for Non-significant Risk determination by the Sponsor-Investigator.*

## Preclinical Data

*Summarize the available non-clinical data (published or available unpublished data) that could have clinical significance.*

## Clinical Data to Date

*Summarize the available clinical study data (published or available unpublished data) with relevance to the protocol under construction -- if none is available, include a statement that there is no available clinical research data to date on the investigational product.*

## Treatment Rationale and Risk/Benefits

*Describe the rationale used for selection of the treatment rationale for the protocol under construction. This should be based on non-clinical and clinical data available to date Discuss why the risks to subjects are reasonable in relation to the anticipated benefits and/or knowledge that might reasonably be expected from the results.*

# Study Objectives

*Describe the overall objectives and purpose of the study. This should include both primary and any secondary objectives, e.g.:*

*Primary Objective*

*To assess the efficacy of XXXX on decreasing infarct size as measured by Sestamibi scanning.*

*Secondary Objective*

*To assess the safety and tolerability of two treatments using iovera° in subjects with acute lumbar pain.*

# Study Design

## General Design

*Include:*

* The type/design of the study (e.g., randomized, double-blind, parallel group, etc.)
* A schematic diagram of the trial design, procedures and stages is advisable
* Expected duration of subject participation
* A summary description of the sequence and duration of all trial periods including follow-up, if any

## Primary Study Endpoints

*Describe the primary endpoint to be analyzed in the study (e.g. could be safety or efficacy, depending on the main objective of the study).*

## Secondary Study Endpoints

*Describe any secondary endpoints to be analyzed in the study*

## Primary Safety Endpoints

*All studies should include the primary safety endpoints to be measured. If the primary objective of the study is a safety study and therefore the Primary Endpoint(s) of the study are safety endpoints, then it should be noted in section 3.2 above and this subsection 3.4 can be deleted.*

# Subject Selection and Withdrawal

## Inclusion Criteria

*Create a numbered list of criteria subjects must meet to be eligible for study enrollment (e.g. age, gender, target disease, concomitant disease if required, etc.) Generally should include items such as: “subjects are capable of giving informed consent”, or if appropriate, “have an acceptable surrogate capable of giving consent on the subject’s behalf.”*

## Exclusion Criteria

*Create a numbered list of criteria that would exclude a subject from study enrollment. If appropriate, should generally include that subjects cannot be homeless persons, or have active drug/alcohol dependence or abuse history. If exposure to certain medications or treatments at screening is prohibited, that must be noted in the exclusion criteria—if these are also prohibited concomitant medications during the study period that should be noted here as well.*

## Subject Recruitment and Screening

*Describe how subjects will be recruited for the study, e.g. from investigator or sub-investigator clinical practices, referring physicians, advertisement, etc. Note in this section that information to be disseminated to subjects (handouts, brochures, etc.) and that any advertisements must be approved by the EC/IRB for the site; include a sample of such information in the attachment section of the protocol. Also in this section, list any screening requirements such as laboratory or diagnostic testing necessary to meet any noted inclusion or exclusion criteria (greater detail of timing, etc. can be included later in section 6 “Study Procedures” section of the protocol).*

## Early Withdrawal of Subjects

### When and How to Withdraw Subjects

*Describe the scenarios under which a subject may be withdrawn from the study prior the expected completion of that subject (e.g. safety reasons, failure of subject to adhere to protocol requirements, subject consent withdrawal, disease progression, etc.) Also, if abrupt termination of study treatment could affect subject safety (e.g. in an antihypertensive study, abrupt withdrawal without other intervention might cause hypertensive rebound), describe procedure to transition subject off the study treatment or to alternate therapy.*

# Study Device

## Description

*This section should be a very brief synopsis of section 1.2 “Device Description”, along with how the how the device will appear.*

## Treatment /Procedure Description

*Describe treatment procedures and treatment duration. . Fully describe how the study treatment is to be administered.*

## Method for Assigning Subjects to Treatment Groups

*Describe how a randomization number and associated treatment assignment will be made. This could be selection of a sequentially numbered device, or communication with a randomization center that assigns a number associated with a specific treatment device, etc.*

## Subject Compliance Monitoring

*Describe how the study team will assess and track subject compliance with the study treatment regimen, and what procedures must be followed for any subject who is significantly non-compliant with the study treatment regimen.*

## Prior and Concomitant Therapy

*In this section, describe:*

* What prior and/or concomitant medical therapy will be collected (if applicable).
* Which concomitant medicines/therapies (including rescue therapies) are permitted during the study
* Which concomitant medicines/therapies are not permitted during the study (if applicable)

## Blinding of Study Device(s)

*Describe how the device is blinded (refer back to Section 8.4 “Unblinding Procedures”), if applicable.*

## Receiving, Storage, Dispensing and Return

### Receipt of Devices and Supplies

*Describe how device will be obtained i.e. what entity will ship the device to the investigative site, and to what location at the site.*

Upon receipt of the of the study treatment supplies, an inventory must be performed and a device receipt log filled out and signed by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study devices in a given shipment (active device or comparator) will be documented in the study files. The investigator must notify study sponsor of any damaged or unusable study treatments that were supplied to the investigator’s site.

### Storage

*Describe storage temperature requirements, whether supplies must be protected from light, and the location of the supplies. Describe any special handling requirements during storage.*

### Dispensing of Study Devices

*Describe how the devices will be assigned to each subject and administered. This section should include regular device reconciliation checks.*

### Return or Destruction of Study Device

*This section should note the procedures for final reconciliation of the site’s device supply at the end of the study, and whether study devices are to be shipped back to a source or destroyed on site.*

At the completion of the study, there will be a final reconciliation of devices shipped, devices used, and devices remaining. This reconciliation will be logged on the device reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study devices. Devices destroyed on site will be documented in the study files.

# Study Procedures

*In this section, describe all the procedures and treatments required at each visit, broken out by visit. Create a study procedures flowchart/table that describes the activities and procedures to be followed at each visit. Include this flowchart/table in the Attachment section and refer to that attachment in this section.*

## Visit 1

## Visit 2

## etc.

# Statistical Plan

## Sample Size Determination

*Describe the statistical methods for determining the sample size for the study*

## Statistical Methods

*Summarize the overall statistical approach to the analysis of the study. The section should contain the key elements of the analysis plan, but should not be a reiteration of a detailed study analysis plan. The full Statistical Analysis Plan can then be a “stand-alone” document that can undergo edits and versioning outside of the protocol and therefore not trigger an IRB re-review with every version or edit –AS LONG AS THE KEY ELEMENTS OF THE ANALYSIS PLAN DO NOT CHANGE.*

*Be clear on primary as well as any applicable secondary analyses*

## Subject Population(s) for Analysis

*This section should be very specific in defining the subject populations whose data will be subjected to the study analysis – both for the primary analysis and any applicable secondary analyses. Examples of such populations include:*

* *All-randomized population: Any subject randomized into the study, regardless of whether they received study device*
* *All-treated population: Any subject randomized into the study that received at least one treatment with the study device*

# Safety and Adverse Events

## Adverse Event Reporting

## Information regarding occurrence of adverse events will be captured throughout the study. Duration (start and stop dates and times), severity/grade, outcome, treatment and relation to study device will be recorded on the case report form (CRF).

The study Investigator will evaluate, characterize and record in the CRF all adverse events (AEs) occurring in all subjects from the time of enrollment to study exit (or premature withdrawal). AEs will be followed until resolution or study exit, whichever comes first. AEs may be reported spontaneously by the subject or detected by the Investigator. AEs should be evaluated for diagnoses not just symptoms (i.e., “angina”, not “chest pain”).

* Adverse Event Definitions

An **adverse event** (AE) is any untoward medical occurrence, independent of its association with the investigational device. AEs also include any adverse laboratory signs or physical exam findings.

A **serious adverse event** (SAE[[1]](#footnote-1)) is any AE that:

* led to a death,
* led to a serious deterioration in the health of the subject that:
* resulted in a life-threatening illness or injury,
* resulted in a permanent impairment of a body structure or a body function,
* required in-patient hospitalization or prolongation of existing hospitalization,
* resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function
* or led to fetal distress, fetal death or a congenital abnormality or birth defect.

A **device-related SAE** is an event meeting the SAE definition above that is also rated as probably or definitely related the investigational device. No device-related SAEs have been reported in prior studies of iovera°.

Note that an elective or pre-planned hospitalization for a condition that did not worsen during the study is not an AE.

* AE Severity and Relatedness

Each AE occurring in the study will be characterized by the study Investigator as to severity (Table 1) and relatedness (Table 2).

Table 1. AE Severity Grading System.

|  |  |
| --- | --- |
| **Severity Grade** | **AE Description** |
| Mild | AE is transient and easily tolerated by the subject, even if it causes discomfort |
| Moderate | AE causes the discomfort and interrupts usual activities |
| Severe | AE causes considerable interference with usual activities and may be incapacitating or life-threatening |

Table 2. AE Relatedness Grading System.\*

|  |  |  |
| --- | --- | --- |
| **Grade** | **Relationship of AE to study device** | **Description** |
| 5 | Definite | An event that follows a reasonable temporal sequence from administration of the study device; that follows a known or expected response pattern to the study device; and that is confirmed by improvement on stopping. |
| 4 | Probable | An event that follows a reasonable temporal sequence from administration of the study device; that follows a known or expected response pattern to the study device; and that is unlikely to have been caused by concurrent/underlying illness or other drugs, procedures, or other causes. |
| 3 | Possible | An event that follows a reasonable temporal sequence from administration of the study device; that follows a known or expected response pattern to the study device; but may have been caused by concurrent/underlying illness, drugs, procedure, or other causes. |
| 2 | Unlikely | An event that does not follow a reasonable temporal sequence from administration of the study device; that does not follow a known or expected response pattern to the study device, or most likely was caused by concurrent/underlying illness, drugs, procedure, or other causes, because of their known effects. |
| 1 | Not related | An event almost certainly caused by concurrent/underlying illness, drugs, procedure, or other causes. |

\*Note that an AE occurring before treatment with the study device will be categorized as unrelated to the study device.

An **unanticipated adverse device effect** (UADE) is any SAE that is caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application).

* Adverse Event Reporting

Investigators must report all SAEs to myoscience and governing IRB within 24 hours or according to local IRB guidances. The Investigator should be able and willing to provide further information on the specific event when requested by myoscience. If the Investigator learns of an SAE that occurs within 1 month after the subject completes the study, he/she should notify the myoscience. Investigators must also report all AEs and SAEs to the governing IRB as determined by that IRB.

Prompt AE evaluation:

* protects the safety of study subjects;
* aids in understanding the overall safety profile of the device;
* prompts, if necessary, modification to the study protocol
* allows improvements in study design or procedures; and
* adheres with standard good clinical practices.

## Unblinding Procedures

*While the safety of the subject always comes first, it is still important to seriously consider if unblinding the study therapy is necessary to ensure a subject’s safety. This section should clearly describe the procedures for unblinding study therapy on a subject, including documentation of this in the subject’s source document. For investigators, other than the sponsor-investigator, state that the investigator must inform the sponsor of all subjects whose treatment was unblinded – and describe the timelines for such reporting. In most cases, the unblinding will be part of managing an SAE, and will be reported with the SAE, however, in cases where unblinding was not associated with an SAE, such actions should be reported in a timely manner. While there is no regulation governing this timeline, it is suggested to use the same timeline requirements for investigator reporting of SAEs, (i.e. notification of sponsor within 24 hours by phone or fax, followed by a written narrative of the event within 48 hours.)*

## Stopping Rules

*In studies with a primary safety endpoint or studies with high risk to study subjects, rules should be developed that clarify the circumstances and procedures for interrupting or stopping the study.*

## Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site.

# Data Handling and Record Keeping

## Confidentiality

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). Those regulations require a signed subject authorization informing the subject of the following:

* What protected health information (PHI) will be collected from subjects in this study
* Who will have access to that information and why
* Who will use or disclose that information
* The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization.

## Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects’ diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

## Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write “N/D”. If the item is not applicable to the individual case, write “N/A”. All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

## Records Retention

*For FDA-regulated studies the following sample language is appropriate:*

It is the investigator’s responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

# Study Monitoring, Auditing, and Inspecting

## Study Monitoring Plan

This study will be monitored according to the monitoring plan in Attachment \_\_\_. The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

## Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the funding sponsor, government regulatory bodies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

# Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 812 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the funding sponsor before commencement of this study. The investigator should provide a list of EC/IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See Attachment \_\_\_ for a copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a subject, using the EC/IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

# Study Finances

## Subject Stipends or Payments

*Describe any subject stipend or payment here. If there is no subject stipend/payment, delete this section.*

# Publication Plan

*If, in addition to the sponsor-investigator, other investigators are involved with the study, identify who holds the primary responsibility for publication of the results of the study. Also define the need to first obtain approval from the primary responsible party before any information can be used or passed on to a third party.*

.

# References

*This is the bibliography section for any information cited in the protocol. It should be organized as any standard bibliography.*

1. Author, Title of work, periodical and associated information.
2. Author, Title of work, periodical and associated information.

# Attachments

*This section should contain all pertinent documents associated with the management of the study. The following list examples of potential attachments:*

* Sample Consent Form
* Study Procedures Flowchart/Table
* Statistical Analysis Plan
* Monitoring Plan

1. Definition from ISO14155:2011 [↑](#footnote-ref-1)