Title of the Research Study

 Protocol Number

Protocol Number

Protocol Version

Version Date

Version #

IDE Number:

IDE Holder:

**PRINCIPAL INVESTIGATOR:**

*Name*

*Department*

*Telephone Number*

*Email Address*

Confidentiality Statement:

**Preface**

**(Remove this Preface before finalizing the study protocol)**

* Use this protocol template for an-investigator initiated protocol using a device (approved or unapproved) in one or more persons to evaluate the safety or effectiveness of that device for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease. This includes in-vitro diagnostic devices, mobile medical applications, and companion diagnostic devices.
* Once completed, upload your protocol in the “Basic Information” screen in the IRES IRB system.
* Enter protocol specific text in the sections that are applicable. Put “Not Applicable or N/A” for the sections that do not apply.
* When making changes, update the version number and date in the header to ensure proper version control.
* Please refer all questions regarding the use of this protocol template to hrpp@yale.edu or 203-785-4688.

**How to Use This Template**

**Green text box: provides section-specific guidance to aid in protocol writing. This entire box should be deleted prior to finalizing the protocol.**

*Blue, italicized text = example text: This text is provided to assist in protocol writing and should be modified to suit your specific protocol. Example text is not available for all sections.*

**REVISION HISTORY:**

Include the IRB approved protocol version number and date for each revision of the protocol. All version history should remain in the table and never be deleted. The oldest IRB approved version of the protocol should be listed on the top row. The most recent IRB approved version should be listed on the bottom row.

|  |  |
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| **Revision #** | **Version Date** |
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# Synopsis

Instructions: Complete the synopsis last, ensuring that it matches with the information found in the body of the document. Information in sections should be high-level, introducing the study; save the detailed information for the body. Don’t put information in the synopsis that is not in the body.

|  |
| --- |
| **Primary Objective**State the main purpose for performing the study. It should be clear, detailed but limited in scope. Keep in mind the primary objective will help determine the sample size. |
| **Secondary Objective (if applicable)**Identify any secondary objectives, which may or may not be hypothesis driven or dependent on the primary objective. |
| **Study Duration** |
| **Study Design** Include a high-level description of the study design. *This is a prospective, non-randomized clinical study to evaluate the effectiveness of transcutaneous electrical nerve stimulation (TENS) on chronic pain patients.* |
| **Number of Study Sites**Include the number and location of all study sites.  |
| **Study Population**Define the study population, source of the participants, and selection rationale. Study subjects should be representative of the population of interest.Provide a brief description of the study population (e.g., healthy/sick, children/adult, inpatient/outpatient, demographic groups), the characteristics of different study groups, if applicable, and the source of participants. Do not list inclusion/exclusion criteria here, as these will be listed in the upcoming sections.  |
| **Number of Participants** |
| **Primary Outcome Variables** |
| **Secondary and Exploratory Outcome Variables (if applicable)** |

# Abbreviations

|  |  |
| --- | --- |
| **Abbreviation**  | **Explanation** |

# Glossary of Terms

|  |  |
| --- | --- |
| **Glossary** | **Explanation** |

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# Introduction

## Introductory Statement

This document is a protocol for a human research study. The purpose of this protocol is to ensure that this study is to be conducted according to ICH GCP guidelines, and according to CFR 21 Part 812, other applicable government regulations, and Institutional research policies and procedures.

# Background

### Device Preclinical Experience

Explain the mechanism of action and summarize the results of all prior pre-clinical studies. Include information to support safety issues and rationale for proposed schedule.

### Device Clinical Experience

Summarize the results of prior clinical studies and your own clinical experience using the device off label to treat patients if applicable. Include rationale for the schedule and exposure (e.g., use of the device) in the proposed study.

**Note:** If one or more study procedures using FDA approved or cleared devices are considered standard of care that a patient could get even if not in the study, but is not actually a planned procedure for that individual patient, then standard of care research activities should be included as study procedures. If, however, regardless of whether the subject is enrolled in the study, the subject will be undergoing one or more procedures (usually this is included in the eligibility criteria e.g. patient is scheduled to undergo this procedure regardless of whether enrolled in the study), then the study is an observational data collection study about the procedure(s) and risks associated with the procedure(s) are not research related. What matters is whether these procedures are protocolized, or in other words, selected by the PI or sponsor to answer a research question rather than selected independently by the patient’s physician solely for that patient’s benefit. If the former, they are part of research and associated risks part of the research. If the latter, they are not part of the research, associated risks are not part of the research risks, and the study is then observational not interventional.

## Background/prevalence of research topic

This section should contain a background discussion of the condition under investigation.

Include:

• The name and description of the health problem the study will evaluate

• A summary of relevant research and gaps in the research literature, and if applicable, how the research study addresses those

• Discussion of important literature and data that are relevant to the study, explain the problem and the importance of the study (include key supporting reference citations using the references tool)

• Describe any applicable clinical, epidemiological, or public health background or context of the study.

# Rationale/Significance

## Problem Statement

State the existing problem and main reason for doing the study.

## Purpose of Study/Potential Impact

Describe the main purpose of the study and the impact this research could have on the stated problem, such as disease prevention, disease diagnosis, treatment, money savings or quality of life improvements.

### Potential Risks

Describe potential risks (physical, psychological, distress due to study participation, social, economic, legal, issues with insurability, employability or breach of confidentiality, etc.) to subjects or others. The device manual or Instructions for Use should be the primary source of information of risks of the device. Include any procedures to minimize risks.

### Potential Benefits

Describe expected benefits to research subjects, society and/or science and their likelihood. If there are no expected benefits, this should be stated.

# Study Objectives

## Hypothesis

Include a clearly defined hypothesis, if relevant, and list the key questions the study is expected to answer. Be detailed, clear and as specific as possible.

## Primary Objective

State the main purpose for performing the study. It should be clear, detailed but limited in scope. Keep in mind the primary objective will help determine the sample size.

*The primary objective of this study is to determine whether the [device] reduces, increases, etc. outcome measure [insert outcome measure] in population [insert population description].*

## Secondary Objectives (if applicable)

Identify any secondary objectives, which may or may not be hypothesis driven or dependent on the primary objective. Add exploratory objectives if applicable.

*The secondary objective[s] of this study is [are] to [insert goal: determine, describe, understand, etc.] whether the [insert exposure, presenting sign, comorbidity, treatment option] reduces, increases, etc. outcome measure [insert outcome measure].*

# Study Design

## General Design Description

Describe the study type, which should be based on the proposed objectives and availability of resources. Include rationale for study design and measures to avoid or reduce bias, such as blinding and/or randomization. Specify, for example, whether the study is randomized or non-randomized, blinded or non-blinded and include the phase (1, 2, 3 or 4). Consult with a biostatistician if needed.

Include a study schema/flow-chart that graphically diagrams the overall study.

### Study Date Range and Duration

State the expected length of the study from recruitment to any follow-up.

### Number of Study Sites

Include the planned number of all study sites.

## Outcome Variables

### Primary Outcome Variables

Explain the variables that will used to assess the primary objective. They should be precise, accurate and reliable. Include any rationale.

### Secondary and Exploratory Outcome Variables (if applicable)

Explain the endpoints that will be used to assess any secondary objectives. They should be precise, accurate and reliable. Include the rationale. Add Exploratory endpoints if applicable.

## Study Population

Define the study population, source of the participants, and selection rationale. Study subjects should be representative of the population of interest. Describe any vulnerable populations specifically.

*Participants with [medical condition] of [insert level of severity] severity and [other symptoms/disease specific criteria] and/or healthy volunteers aged [insert age].*

### Number of Participants

Include the number of people that will be screened and the number of participants that are anticipated to make it through screening and enrolled. For multi-center protocols, identify both overall total for study and numbers for each site.

### Eligibility Criteria/Vulnerable Populations

Identify who determines eligibility, and inclusion/exclusion criteria. List only the eligibility criteria absolutely necessary for the study as a bulleted or numbered list. The study population should be appropriate for clinical trial phase and the development stage of the study intervention. Given the continuing challenges in achieving clinically relevant demographic inclusion in clinical trials, it is important to focus on clinically relevant potential participants at the earliest stages of protocol development. Therefore, it is essential that the population’s characteristics be considered during the trial planning phase to ensure the trial can adequately meet its objectives and provide evidence for the total population that will potentially utilize the study intervention under evaluation (e.g., elderly and pediatric populations, women, and minorities). Describe any vulnerable populations specifically and rationale for including or excluding them from the study.

• The eligibility criteria should provide a definition of participant characteristics required for study entry/enrollment.

• If participants require screening, distinguish between screening participants vs enrolling participants. Determine if screening procedures will be performed under a separate screening consent form.

• The risks of the study intervention should be considered in the development of the inclusion/exclusion criteria so that risks are minimized.

• The same criterion should not be listed as both an inclusion and exclusion criterion (e.g., do not state age >18 years old as an inclusion criterion and age ≤18 years old as an exclusion criterion).

• Identify specific laboratory tests or clinical characteristics that will be used as criteria for enrollment or exclusion.

• If reproductive status (e.g., pregnancy, lactation, reproductive potential) is an eligibility criterion, provide specific contraception requirements (e.g., licensed hormonal or barrier methods).

• If you have more than one study population, please define the common inclusion and exclusion criteria followed by the specific inclusion and exclusion criteria for each subpopulation.

**Inclusion criteria** are characteristics that define the population under study, e.g., those criteria that every potential participant must satisfy, to qualify for study entry. Provide a statement that individuals must meet all of the inclusion criteria in order to be eligible to participate in the study and then list each criterion. Women and members of minority groups must be included in accordance with the NIH Policy on Inclusion of Women and Minorities as Participants In Research Involving Human Subjects.

Some criteria to consider for inclusion are: provision of appropriate consent and assent, willingness and ability to participate in study procedures, age range, health status, specific clinical diagnosis or symptoms, background medical treatment, laboratory ranges, and use of appropriate contraception. Additional criteria should be included as appropriate for the study design and risk.

*[In order to be eligible to participate in this study, an individual must meet all of the following criteria:*

1. *Provision of signed and dated informed consent form*
2. *Stated willingness to comply with all study procedures and availability for the duration of the study*
3. *Male or female, aged <specify range>*
4. *In good general health as evidenced by medical history or diagnosed with <specify condition/disease> or exhibiting <specify clinical signs or symptoms or physical/oral examination findings>*
5. *<Specify laboratory test> results between <specify range>*
6. *Ability to take oral medication and be willing to adhere to the <study intervention> regimen*
7. *For females of reproductive potential: use of highly effective contraception for at least 1 month prior to screening and agreement to use such a method during study participation and for an additional <specify duration> weeks after the end of <study intervention> administration*
8. *For males of reproductive potential: use of condoms or other methods to ensure effective contraception with partner*
9. *Agreement to adhere to Lifestyle Considerations (see section 5.3) throughout study duration]*

**Exclusion criteria** are characteristics that make an individual ineligible for study participation. Provide a statement that all individuals meeting any of the exclusion criteria at baseline will be excluded from study participation and then list each criterion. If specific populations are excluded (e.g., elderly or pediatric populations, women or minorities), provide a clear and compelling rationale and justification, to establish that inclusion is inappropriate with respect to the health of the participants or the purpose of the research. Limited English proficiency cannot be an exclusion criterion.

Some criteria to consider for exclusion are: pre-existing conditions or concurrent diagnoses, concomitant use of other medication(s) or devices, known allergies, other factors that would cause harm or increased risk to the participant or close contacts, or preclude the participant’s full adherence with or completion of the study. Additional criteria should be included as appropriate for the study design and risk.

Include a statement regarding equitable selection or justification for excluding a specific population.

*[An individual who meets any of the following criteria will be excluded from participation in this study:*

1. *Current use of < specify disallowed concomitant medications>*
2. *Presence of <specific devices (e.g., cardiac pacemaker)>*
3. *Pregnancy or lactation*
4. *Known allergic reactions to components of the <study intervention>, <specify components/allergens>*
5. *Febrile illness within <specify time frame>*
6. *Treatment with another investigational drug or other intervention within <specify time frame>*
7. *Current smoker or tobacco use within <specify timeframe>*
8. *< Specify any condition(s) or diagnosis, both physical or psychological, or physical exam finding that precludes participation>]*

# Methods

## Treatment – Device

### Intended Use for Device (provide the following information for each device being investigated in the study)

Describe the intended use of the device.

Include test product or device identity (i.e., proprietary and generic names), and FDA-clearance or approval status if applicable. The source of any comparator product should also be included and any modifications of the product from their usual commercial state should be noted. State the intended use of the device if approved, and if the intended use in the study differs from its approved/cleared use describe how.

### Device Administration and Schedule

Describe the schedule and administration of the device. Include any procedures for device preparation, changes for safety or efficacy reasons, tapering of device administration at the end of the study, participant instructions, and tracking compliance and handling non-compliance.

### Method of Assignment/Randomization (if applicable)

If applicable, explain the randomization/assignment process.

### Device Calibration

Describe necessary calibration process, schedule, and documentation of record required throughout study.

### Storage Conditions

Describe storage requirements (temperature, protection from light, etc.) for the device, method of sterilization (if applicable, maintenance considerations. Include procedures for ensuring accountability and return, destruction or other disposition at the end of the study.

### Concomitant therapy

Specify any concomitant medications permitted or explicitly forbidden during the study, including time periods. If none, state that there are no restrictions.

### Restrictions

Specify any relevant restrictions, warnings or precautions, including time periods. If none, state there are no restrictions.

## Assessments

### Efficacy

Specify parameters (such as procedures, lab tests, assessments, etc.) used to evaluate the efficacy of the intervention, including methods and timing for assessing, recording and analysis.

Include any questionnaire administration and identify the questionnaire to be used for the study related assessment. State how these assessments contribute to the overall study aims.

Include as appendices copies of each questionnaire.

### Safety

Specify parameters (such as procedures, lab tests, etc.) used to monitor and evaluate the safety of the device according to the objectives of the study, including methods and timing for assessing, recording and analysis.

### Adverse Events Definition and Reporting

Specify how adverse events will be defined and assessed for causality (relationship to intervention) and graded for severity (provide an adverse event grading scale).

The relationship, severity, and expectedness (including level and frequency) of an adverse event should be assessed based on previous experience with the intervention and reasonable judgment.

This section should also describe:

* Time frame for collecting adverse events (i.e. from consent or time of start of study until end of intervention or follow-up).
* Frequency and process for eliciting adverse event information from research subjects (include how often, by whom and what records will be reviewed to collect adverse events).
* Specific management plans for expected or unexpected adverse events. Expectedness of adverse events should also be described in informed consent and be consistent with the protocol.
* AE reporting procedures (including how often, by whom and to who adverse events will be reported.

Ensure reporting timelines meet IRB and FDA requirements. Refer to Adverse Event Reporting in the Resource Center section for details.

A sponsor who conducts an evaluation of an unanticipated adverse device effect under §812.46(b) shall report the results of such evaluation to FDA and to all reviewing IRB's and participating investigators within 10 working days after the sponsor first receives notice of the adverse effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests.

An unanticipated adverse device effect means any serious adverse effect on health or safety or any life-threatening problem or death 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, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. (21 CFR 812.3(s))

### Pharmacokinetics (if applicable)

If pharmacokinetic testing will be done, include timing, frequency, amount of specimens required and whether or not there will be an additional consent form for this testing.

### Biomarkers (if applicable)

If biomarker testing will be done, include timing, frequency, amount of specimens required and whether or not there will be an additional consent form for this testing.

## Study Procedures

Investigators are required to perform research as written in the protocol, so this section should be written clearly and carefully to minimize deviations.

Identify all procedures considered experimental, those performed exclusively for research purposes and those that would occur regardless of the research (i.e. standard of care). Include all observations that will take place during the study, and Study Schedule listing study procedures (visit by visit) with timing intervals to provide a summary for study team and reviewers.

### Study Schedule

Specify total number of expected visits, including consent and screening, on study visits and follow-up. If possible, provide a reasonable time estimate for each visit. Include a table of events as an appendix or table at end of application.

Insert a tabular Schedule of Events here or appendix as well.

### Informed Consent

Confirm that provisions are in place for seeking IRB-approved informed consent of participants or legally authorized representatives (LAR), and that the process will minimize undue influence or coercion and offer sufficient time for review.

### Screening

Describe the screening process including who will perform screening procedures. Include specific procedures to be completed and timeframe.

### Enrollment

Identify who will enroll the subjects in the study and how this process will take place (for instance, after they have been consented, screened and meet eligibility criteria).

### On Study Visits

Describe what study procedures will be conducted during each study visit as a bulleted itemized list. Refer to the Schedule of Events and the sections of the protocol describing efficacy and safety assessments. Include timing and approximate length of the visits.

### End of Study and Follow-up

Describe end of study and follow-up procedures (such as collection of adverse events, vital status, etc.). Include any follow-up procedures for participants who withdraw from the study early.

### Removal of subjects

State criteria, procedures and documentation instructions for withdrawing a subject early from the study. Note that subjects may withdraw voluntarily at any time for any reason.

For interventional studies involving drugs/biologics/device the documentation should also include procedures for how the subject will transition from the research to routine care, if applicable.

## Statistical Method

### Statistical Design

Describe the overall statistical design of the study and the approach for the analysis of the study data.

### Sample Size Considerations

Describe the statistical methods for determining the sample size and power calculations for the study.

### Planned Analysis

#### Primary Analyses

Explain how data will be analyzed to evaluate the stated primary study objective.

#### Secondary Objectives Analyses

Explain how data will be analyzed to evaluate each of the secondary study objectives, if applicable.

#### Safety

If evaluation of safety is not already either a primary or secondary objective for the study, specify analysis to evaluate safety.

#### Analysis of Subject Characteristics

Specify descriptive analysis to define subject population(s).

#### Interim Analysis (if applicable)

If an interim analysis will be done, explain the rationale, timing, and impact to the study. Include any stopping rules that would determine if the study should be discontinued.

#### Health economic evaluation

Specify analysis to evaluate heath economic impact, which may include net health benefits, cost-effectiveness, cost-utility, and cost benefits of the intervention.

#### Other

Specify any additional analysis that will be done.

### Subsets and Covariates

Specify analysis of subsets or covariates. Explain known or suspected confounding variables, how they may affect data or outcomes and why certain confounding factors cannot be screened out. Include any calculations to evaluate confounding variables, and methods to minimize them.

### Handling of Missing Data

Describe how missing outcome data will be handled in regards to analysis.

#  Trial Administration

##  Ethical Considerations: Informed Consent/Assent and HIPAA Authorization

This section should include any applicable ethical considerations. They should also be addressed in the Informed Consent form. This section should include a statement that the study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

Describe the following:

* Any possible deception.
* Rationale if payment will be provided for participation.
* Any sensitive data that may be collected and how it will be protected.
* Any possibility that a previously unknown condition (disease, genetic disposition, etc.) will be discovered as the result of the study procedures and how this will be handled.
* Any information that may be added to the subject's permanent medical records with rationale.

## Institutional Review Board (IRB) Review

Include a statement about IRB oversight and review throughout the study. This may be institution or sponsor specific.

*The protocol will be submitted to the IRB for review and approval. Approval of the protocol must be obtained before initiating any research activity. Any change to the protocol or study team will require an approved IRB amendment before implementation. The IRB will determine whether informed consent and HIPAA authorization are required.*

*The IRB will conduct continuing review at intervals appropriate to the degree of risk, but not less than once per year.*

*A study closure report will be submitted to the IRB after all research activities have been completed.*

*Other study events (e.g. data breaches, protocol deviations) will be submitted per [insert institution's] IRB's policies.*

## Subject Confidentiality

State the provisions to protect the privacy of participants. This may be institution or sponsor specific.

*Subject confidentiality is held in strict trust by the research team. Subject medical record review will be limited to the just the elements needed to complete the study. Only authorized HIPAA and GCP trained study team members will be allowed to extract research data from medical records and enter it into [insert research database name]. No direct subject identifiers will be entered into [insert research database name].*

*Each subject will be assigned a unique study number. A master list linking the unique study number to the human subject will be maintained in a locked drawer in [insert location].*

## Deviations/Unanticipated Problems

Explain how unanticipated problems that may occur during the study will be handled, communicated to the IRB, sponsor, and FDA, if applicable.

This section should also address how Protocol Deviations will be managed during the study including plans for detecting, reviewing, and reporting deviations from the protocol.

*If the study team becomes aware of an anticipated problem (e.g. data breach, protocol deviation), the event will be reported to the IRB by [insert mechanism].*

## Data Collection

Describe the data source, timing for collection, how it will be collected (Data Collection Form should be provided as an appendix), and who can access it and how long it will be retained. Explain procedures for handling or destroying data at the end of the study and any plans for de-linking, coding or de-identifying collected information.

## Data Quality Assurance

Describe the quality control and assurance for the conduct of the study to ensure that Good Clinical Practice is followed. Any steps that will be implemented as part of the study to ensure standardization of the collection of accurate, consistent, complete and reliable data, such as training sessions, monitoring of investigator sites, instruction manuals, use of central laboratory or reading center should be included.

## Study Records

Specify the documents considered study records (regulatory documents, protocols, consents forms, case report forms, subject medical records, surveys, etc.).

## Access to Source

Describe the source documents and how data will be collected from them and incorporated into the database. Specify who will have access and how it may be transferred to any collaborators.

## Data or Specimen Storage/Security

Describe method in which data will be collected, stored (digital, hard copy, etc.) and maintained in a secure manner (encryption, password protection, etc.).

## Retention of Records

Specify how long the study records will be retained. If permission is needed to move or destroy the records, identify the person who will need to be contacted (investigator, sponsor, etc.).

## Study Monitoring

Specify who will monitor the study (third party, sponsor, internal team, etc.), where monitoring will occur and frequency. Describe any related responsibilities and identify anyone who will review the study for accuracy and how often.

## Data Safety Monitoring Plan

Describe the data safety monitoring plan for the study. Examples of DSMPs are available at http://your.yale.edu/policies-procedures/forms/420-fr-01-data-and-safety-monitoring-plans-templates. What is the investigator’s assessment of the overall risk level for subjects participating in this study? If children are involved, what is the investigator’s assessment of the overall risk level for the children participating in this study?

## Study Modification

Describe how any study modifications will be handled. State how and when the protocol will be updated and when the change will be implemented into the study.

## Study Discontinuation

Explain the circumstances under which the study may be discontinued.

## Study Completion

State the completion date of the study and specific instructions for notifying IRB and FDA, if applicable.

## Conflict of Interest Policy

This section should include a description of how the study will manage actual or perceived conflicts of interest. Yale policies require investigators engaged in human subjects research to disclose annually. Read more at https://your.yale.edu/research-support/conflict-interest

*The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership in conjunction with the appropriate conflict of interest review committee has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.*

 *All investigators will follow the applicable conflict of interest policies.*

## Funding Source

Explain how the study will be funded but do not include specific dollar amounts.

## Publication Plan

Describe the requirements and publication policy (of the sponsor, department, university, etc.) and specify who holds primary responsibility for publishing the study results.

# Appendices

|  |  |  |  |
| --- | --- | --- | --- |
| **Appendix #** | **Title** | **Section** | **Topic** |

# List of Tables