***DELETE ALL red and blue INSTRUCTIONS and guidance text before submitting***

Research Study Protocol for:

The study title should be descriptive and concise and match the title on the IRB Application

|  |  |
| --- | --- |
| **Principal Investigator:** | Insert full name of the principal investigator and credentials Include the name of the institution the PI represents  Include PI address and phone number |
| **Sub-Investigators:** |       |
| **Research Site(s):** | Insert the name and address of site(s) where research will be conducted |
| **Sponsor:**  | Insert name, address and phone number of sponsor If investigator is also the sponsor, reflect that information |
| Version Date: |       |

|  |  |
| --- | --- |
|  |  |

BACKGROUND and PRELIMINARY DATA

Background and Rationale

* Reference the literature searches that confirm or support the hypothesis
* Describe the background of the study and what is known about the topic you choose to study
* Provide the rationale for conducting the study and the knowledge you hope to achieve

Preliminary Data

Discuss what has been done in trials thus far *(i.e., A feasibility study conducted in \_\_\_\_ served as the foundation of a clinical study involving \_\_\_\_\_\_\_\_. This study was a randomized clinical study involving \_\_\_ participants for the treatment of \_\_\_\_. Further confirmation of results was demonstrated in \_\_\_\_.)*

OTHER RELATED STUDIES

*(i.e., A recent case series investigates the use of \_\_\_ for the treatment of \_\_\_\_. This report demonstrated that in these conditions, \_\_\_\_\_ was safe for \_\_\_\_. In addition, a proof-of-concept case series was performed in \_\_\_ to evaluate the safety and ability of \_\_\_\_. There were no \_\_\_\_ related adverse events.)*

PURPOSE and OBJECTIVES

Purpose

*(i.e., The purpose of this study is to determine if \_\_\_\_ can safely/effectively be used in (or to treat) \_\_\_\_ in \_\_\_\_\_\_.)*

Primary Aim

State your hypothesis or key research questions(s); then state the primary aim. *(i.e., The primary objective of this study is to determine whether the \_\_\_\_\_\_ can safely and effectively \_\_\_\_\_\_\_\_. The primary outcome variables include \_\_\_\_ and will be measured by \_\_\_\_.)*

**Secondary Aim** *(Remove if not applicable)*

*(i.e., The secondary objective is to determine if \_\_\_\_ following \_\_\_\_ is sufficient to enable \_\_\_\_.)*

**STUDY DESIGN and METHODOLOGY**

The scientific integrity of the study and the credibility of the study data depend substantially on the study design and methodology. The design of the study should include information on the type of study, the research population or the sampling frame, and who can take part (e.g., inclusion and exclusion criteria, withdrawal criteria etc.), and the expected duration of the study.

The methodology section is the most important part of the protocol. It should include detailed information on the interventions to be made, procedures to be used, measurements to be taken, observations to be made, laboratory investigations to be done etc. If multiple sites are engaged in a specified protocol, methodology should be standardized and clearly defined.

Standardized and/or documented procedures/techniques should be described and bibliographic references, if not provided earlier should be provided. Instruments which are to be used to collect information (questionnaires, FGD guides, observation recording form, case report forms etc.) must also be provided.

In the case of a randomized controlled trial, additional information on the process of randomization and blinding (if applicable), description of stopping rules for individuals for part of the study or the entire study should be noted in this section. Procedures and conditions for breaking codes, etc. should also be described.

**Clinical Procedures**

Be explicit. *(i.e., Up to \_\_\_\_\_ participants who have \_\_\_\_ will be selected to participate in this study. Once enrolled, participants will be randomly assigned to receive one of two possible treatments (specify). Randomization will be performed by \_\_\_\_\_ (describe).)* Discuss the mechanism of action of the drug or device being studied (i.e., what is the intent).

You may provide information in narrative form or use a flow diagram to show study methods.

Figure 1. *Study Design*

**Arm 1 Participants**

\_\_\_ 1x/week for 6 weeks

**Arm 2 Participants**

\_\_\_ 2x/week for 6 weeks

**Reassessment (All Participants)**

4 weeks after \_\_\_\_

**Participants receiving placebo**

will be reassessed 8 weeks post-implementation

**Participants receiving drug/device**

will be reassessed 6 weeks post-implementation

**Post-Treatment Care** (Delete if N/A)

**Clinical Assessments**

*(i.e., At study visits 2, 4, and 6 the \_\_\_\_\_ will be assessed and \_\_\_\_ questionnaires completed. At study visits 8 and 12 a blood draw will be made to assess \_\_\_\_\_.)*

**Figure 2** *Schedule of Clinical Assessments*

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Visit** | **Screening** | **Physical Evaluation** | **Pre-****Blood Draw** | **Baseline** | **Follow-up** | **Follow-up** | **Follow-up** | **Follow-up** | **End of Study Visit** |
| **Timeline** | **Prior to all study activity** | **After screening; prior to dosing** | **1 week prior to baseline** | **Day 0** | **Week 2** | **Week 4** | **Week 6** | **Week 8**  | **Week 12** |
| Informed Consent and Eligibility Confirmation | **X** |  |  |  |  |  |  |  |  |
| Serum collection (CBC, liver, renal panel); pregnancy test for female pts. | **X** |  |  |  |  |  |  | **X** | **X** |
| Radiographs |  | **X** |  |  |  |  |  |  |  |
| EKG |  | **X** |  |  |  | **X** |  |  | **X** |
| Questionnaires |  |  |  | **X** | **X** | **X** | **X** | **X** | **X** |
| Clinical measures |  | **X** |  | **X** | **X** | **X** | **X** | **X** | **X** |
| Biopsy |  |  |  |  | **X** |  |  |  |  |
| AEs will be recorded at every visit |  | 1-2 hrs. |  | 1-2 hrs. | 1-2 hrs. | 1-2 hrs. | 1-2 hrs. | 1-2 hrs. | 1-2 hrs. |

**PATIENT SELECTION**

**Number of Participants and Recruitment**

*(i.e., Up to \_\_\_\_ participants will be enrolled in this study. Participants will be in the study for one year. Active dosing/treatment will be for \_\_\_ days.)* Describe how participants will be recruited and indicate the location and action that will occur. If advertisements will be used, final versions will require submission with the IRB Application. If consent will be mailed to participants for consideration, discuss this also.

**Screening Examination and Timing of Consent Execution**

*(i.e., At the initial screening visit, a complete medical and \_\_\_\_ history will be obtained as well as a \_\_\_\_\_ to evaluate \_\_\_\_. The goals of the study, potential risks, and possible benefits, contact information, use and disclosure information will be explained to all participants prior to conducting any study procedures. Each participant will then sign a written consent statement permitting \_\_\_\_\_\_. Investigators will discuss study participation thoroughly with each participant with ample time for questions and answers. No participant will be admitted into the study until the Informed Consent form is signed. Following consent, participants will have blood draws which will be performed to run laboratory tests to evaluate eligibility for study inclusion.)*

**Inclusion Criteria**

      *(Example below)*

* *Age > 18 years*
* *Male and female*
* *Participant with a history of \_\_\_\_\_\_*
* *Participant must be willing to complete 3 separate questionnaires*
* *Participant must have capabilities to use and access smartphones for collection of some study data*
* *Participant must be able and willing to follow study procedures and instructions*
* *Participant must have read, understood, and signed the informed consent form*

**Exclusion Criteria**

      *(Example below)*

* *Participant anticipates being unable to attend all study visits*
* *Women of child-bearing potential who are pregnant or plan to become pregnant during the course of the study*
* *Have a history of \_\_\_\_\_\_*
* *Have been previously diagnosed with \_\_\_\_\_\_*

**Concomitant Medications**

*(i.e., Participants on significant concomitant drug therapy for system conditions (e.g., cardiovascular disease, renal dysfunction) will not be included in the study. Occasional, short-term use (7-14 days) of analgesics or common cold medication is permitted. Such use of these medications will be reviewed and recorded by the investigator.)*

**TREATMENT and TREATMENT ACCOUNTABILITY**

**Study Medications/Therapeutics**

|  |  |
| --- | --- |
| **Study Medication/Therapeutic** | **Description of Medication/Therapeutic** |
| Amoxicillin | All participants will be prescribed to take 500 mg every 8 hours for 7 days following grafting. For those with allergies to amoxicillin, an appropriate alternative antibiotic will be prescribed. |
| Ibuprofen | In addition to amoxicillin, participants in Arm 1 will take 600 mg every 6 hours for 3 days, beginning day \_\_\_. |

In addition to the sample table above, describe how the drug/device is being supplied. Discuss dosage, model to be used and the method for accountability.

**Risk-Benefit Determination**

Based on information known to date (disease being studied and available treatments) and the profile of the drug/device being used/tested, the PI needs to make a determination about the risks imposed by the treatment and any possible benefits.

***Risk*** is defined as the probability of physical, psychological, social, or economic harm occurring as a result of participation in a research study. Both the probability and magnitude of possible harm in human research may vary from minimal to considerable.

The federal regulations define only "minimal risk."

***Minimal risk*** exists where the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater, in and of themselves, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.
[45 CFR 46.102(i)]

Risk above this standard is more than minimal (moderate, maximal) and that imposes limitations on the conduct of the research and increases the requirements for monitoring. It also requires more stringent approval processes when the research involves children or otherwise vulnerable populations. **Increased risk should be accompanied by the probability of appropriately increased benefits.**

***Benefit*** applies to the potential of the research treatment to ameliorate a condition or treat a disease. This can apply to an individual participant or to a population. In research as in clinical medicine, results cannot be guaranteed but, as a consequence of prior work, a benefit may appear to be a reasonable expectation. Since this is research, an advantage for the treatment groups cannot be presupposed. Since the risks have not been fully evaluated, a statement of individual benefit should be made most cautiously. **The investigator should always distinguish between research and treatment and never coerce the patient into participating in hopes of remission or cure.**

Beneficence means that the intention of the research is for good. Beneficence is demonstrated in the risk-benefit analysis carried out by the PI and confirmed agreement with oversight by the IRB. Of course, many studies offer no personal benefit to the participants, and for these, great care must be taken that the risks are minimized. (AE monitoring, DSMB, external review by expert(s))

The protocol (as well as the associated consent) should include an assessment and judgment of the validity of the research, probability and magnitude of risk (harm) and benefit. The risks presented must be justified.

**STATISTICAL ANALYSIS**

The protocol should provide information on how the data will be managed, including data handling and coding for computer analysis, monitoring and verification. The statistical methods proposed to be used for the analysis of data should be clearly outlined, including reasons for the sample size selected, power of the study, level of significance to be used, procedures for accounting for any missing or spurious data etc. For projects involving qualitative approaches, specify in sufficient detail how the data will be analyzed.

**Summary and General Considerations**

*(i.e., Our study plans to enroll up to 20 participants to evaluate up to \_\_\_, a sample size chosen for feasibility rather than statistical precision. Ten participants with a history of \_\_\_ will be treated with the \_\_\_ and 10 with a history of \_\_\_ will be treated with \_\_\_. Within each of these two groups, participants will be randomly assigned to receive one of two possible treatments. Thus, following stratification of participants based upon the etiology (history) of \_\_\_\_, up to 5 participants will be randomly assigned to one of the four possible participant groups (history of the \_\_\_ arm crossed with the treatment arm). Due to the nature of the treatment group requiring \_\_\_, participant and examiner blinding is not possible.* If blinding is possible, describe the process. *Each participant will receive only one of the two possible treatments.)*

**Analysis Considerations**

Efficacy and safety analyses

*(i.e., Efficacy and safety analyses will be performed for each of the patient groups individually; no direct comparison among the groups is planned. Participants lost to follow-up will be assumed to be missing at random and will not be included in the final analysis. We do not expect there to be a significant amount lost to follow-up in this sample of up to 20 participants. However, because this is*

*a feasibility study, the rate of drop-out by itself is an important parameter to estimate for future studies planning to examine \_\_\_.)*

Demographic analyses

*(i.e., Demographic analyses will be performed on the following parameters at baseline: age, race, gender, medical histories, prior medication use, last visit to a \_\_\_, current use of tobacco, past use of tobacco.)*

Aim 1

*(i.e., Aim 1, efficacy will be measured by the mean clinical \_\_\_ volume and other measures for each of the two patient groups. Each of the two means will be supported with corresponding 95% confidence intervals. With regard to Specific Aim 2, we will compute the proportion (and corresponding 95% confidence interval) of participants in each patient group, which successfully receive \_\_\_. We will also calculate a Kaplan-Meier survival analysis to estimate the rate of loss of any \_\_\_ over time, based on the total number of \_\_\_. However, this study is not powered to assess \_\_\_ survival. We simply plan to gain preliminary information for the generation of descriptive statistics and confirmation that the \_\_\_\_\_\_.)*

Safety analyses

*(i.e., Safety analyses at each post-baseline visit will include reporting of adverse events by body system and by severity and relationship to \_\_\_ therapy as assessed by the investigator.*

**REGULATORY CONSIDERATIONS**

The safety of research participants is foremost. Safety aspects of the research should always be kept in mind and information provided in the protocol on how the safety of research participants will be ensured. This can include procedures for recording and reporting adverse events and their follow-up, for example. It is useful to remember that even administering a research questionnaire can have adverse effects on individuals.

**Study Reporting**

Adverse Events

Any adverse event, including both observed or volunteered problems, complaints, or symptoms, are to be recorded on the Adverse Event CRF. The need to capture this information is not dependent upon whether the adverse event is associated with the use of the study medication. Adverse events resulting from concurrent illnesses or reactions to concurrent medications are also to be recorded. Each adverse event is to be evaluated for duration, intensity and relationship with the study medication or other causes. The intensity of the adverse event will be characterized as mild, moderate, severe, or life threatening as follows:

**MILD** events are usual transient, requiring no special treatment, and do not interfere with the participants daily activities.

**MODERATE** events traditionally introduce a low level of inconvenience of concern to the participant and may interfere with daily activities but are usually ameliorated by simple therapeutic measures.

**SEVERE** events interrupt a participant’s usual daily activity and traditionally require systemic drug therapy or other treatment.

**LIFE THREATENING** events are a threat to life and can require extensive treatment including drug therapy, surgery, hospital admittance and significant recovery time.

When intensity changes occur more frequently than once a day, the maximum intensity for the event should be listed. If the intensity category changes over a number of days, then these mini-events or changes should be recorded separately (i.e. having distinct onset days).

The investigator will use the criteria below as a guideline for determining the relationship of the adverse event to the study therapy:

The event is not related to any concomitant disease, pre-existing condition, other than the therapy, or environmental factors.

One of the following determinations will then be used to document the relationship of the adverse event to the study drug:

NOT RELATED

POSSIBLE

PROBABLE

**Any serious and unexpected adverse event including death due to any cause, which occurs during the investigation, whether or not related to the study article, must be reported immediately (within 24 hours) to the principal investigator and to the IRB.**

A SERIOUS adverse event is one that is fatal, life-threatening, or permanently disabling; one that requires or prolongs hospitalization; or is a congenital anomaly, cancer, or drug overdose.

An UNEXPECTED adverse event is one that is not identified in nature, severity, or frequency in the current Investigational Drug brochure or Informed Consent Document.

Reports of serious or unexpected adverse events will be made immediately to:

 PI Name and contact information

All serious and unexpected adverse events associated with the use of the study medication will be immediately reported to appropriate regulatory agencies by the Principal Investigator.

Internal adverse event reporting will proceed according to IRB policy: [**Unanticipated Problem and Adverse Event Reporting**](https://saml.policymedical.net/policymed/anonymous/docViewer?stoken=f1e162db-50b4-4a1e-a457-797ef23c7500&dtoken=bb7c230f-23d3-4a0b-acec-8cacca33a46d)

**Discontinuation and Replacement of Participants**

*Example:*

* *Any participant found to have entered the study in violation of this protocol will be withdrawn from the study after discussion with the Principal Investigator and this will be documented.*
* *An effort will be made to determine why any participant discontinues the study prematurely. This information will be recorded on the appropriate case report form.*
* *As stated in the informed consent, all participants reserve the right to withdraw from the study at any time.*
* *Any female participant that becomes pregnant during the study, will be withdrawn from the study.*
* *Any participant whose condition changes after entering the study, so that he or she no longer meets the inclusion or exclusion criteria, will be withdrawn from the study.*
* *Any participant who requires the use of an unacceptable concomitant medication will be withdrawn from the study.*
* *The investigator will discontinue any particiapnt from the study if, in the investigator’s opinion, it is not in the participant’s best interest to continue.*
* *The date the participant is withdrawn from the study and the reason for discontinuation will be recorded on the case report form.*
* *When a participant is lost to follow-up, that is, fails to return for study visits, a reasonable effort should be made to contact the participant in order to determine why the participant failed to return. This information will be documented on the CRF. When a participant is withdrawn from the study, regardless of the cause, all evaluations required at the scheduled end of study day should be performed.*

**Data Reporting and Case Report Forms (Data Collection Forms)**

*Example:*

*Data reflecting participant experience with the drug under investigation will be reported to the Principal Investigator and the data recorded on Case Report Forms.*

 *Case Report Forms (CRFs) will be signed and dated by the investigator or a designated representative and filled out in black ink or type written. If an entry on a CRFs requires change, the correction will be made as follows:*

1. *A single line will be drawn through the incorrect entry*
2. *The date will be entered and the change initialed. White-out or erasure on CRF is never to be used.*
3. *If the CRF is electronic document versioning will be instituted to maintain an audit trail for data collection purposes.*

*All fields and blanks must be completed. The following abbreviations will be used when values or answers cannot be provided: NA=not applicable; ND=not done, UNK=not known*

*Completed original CRFs will be collected by the Principal Investigator. CRFs must be submitted for each participant.*

*Data entry will proceed directly from the case report form. The data, as well as group/participant identification, will be made available to the investigator at the conclusion of the study.*

**Study Monitoring**

*Example:*

*The Principal Investigator will regularly (after 1st enrollment and then quarterly, until completion of study) audit all CRFs (data collection forms) and corresponding portions of office, hospital and laboratory records of each study participant. The monitoring will provide the Principal Investigator the opportunity to evaluate the progress of the study, ensure the safety of the participants and to verify the accuracy and completeness of the CRF’s (data collection forms); assure that all protocol requirements, applicable FDA regulations and investigator’s obligations are being fulfilled, and to resolve any inconsistencies in the study records. The Principal Investigator may stop the study if it is observed that the protocol or sound clinical practices are not being followed. The Principal Investigator may exclude participants from the study if review of their medical records indicates violations of the protocol or if there are other reasons to believe that their inclusion would jeopardize the validity of the study.*

Discuss Data Safety Monitoring Board assembly and meeting requirements, if applicable.

**Stopping Rules**

***Special Warnings***

*(i.e., Participants should inform the screener about any possible allergies and current or prior medical conditions or diagnoses.)*

***Precautions for Use***

*(i.e., Participants will be requested to avoid food or drink for one-hour after treatment to avoid \_\_\_ for four weeks. All participants will be advised to contact the Principal Investigator if any adverse reactions, including swelling, bleeding or \_\_\_\_, occurs post-treatment.)*

***Discontinuation Criteria***

*(i.e., Participants who require treatment for acute medical conditions, including use of antibiotics and chronic non-steroidal anti-inflammatory drugs (except for prophylactic doses of aspirin) will be withdrawn from the trial if the Investigator and/or sponsor feel the patient's participation conflicts with his/her care. Medications used to treat chronic conditions must have been initiated at least one month prior to the start of the study. Dosing must be stable and documented at the screening or baseline visit. Any change in dosage or the addition of new medications will be recorded. In addition, the following conditions may lead to discontinuation of a participant from the study:*

* *Concurrent illness*
* *Protocol violation*
* *Withdrawal of consent*
* *Female participants who become pregnant during the course of the trial*

*Participants who discontinue due to a protocol violation will be followed, if they agree, per the protocol.)*

***Handling of Withdrawals***

*(i.e., All participants prematurely discontinued from the trial must be seen, with consent of the participant, for a final evaluation during which full periodontal assessment and oral examination will be performed and the reason for withdrawal recorded. The participant then will be advised to seek medical care as appropriate. In the case of a serious adverse event, the participant will be immediately placed under the care of an appropriate clinician, or if study staff determines the situation is not an emergency, follow-up will be continued until the staff is satisfied an appropriate clinician has managed the health problem. Follow up of an adverse event experience will be up to \_\_\_ days post-occurrence of experience or if the event resolves.)*

***Study Suspension***

*(i.e., The study may be suspended pending discussion with the FDA and reviewing IRB if any of the following events occur:*

*There is one serious adverse event that is at least possibly related to the dosing of \_\_\_)*

**Additional Regulatory Considerations**

***Institutional Review Board (IRB)***

*(i.e., The protocol and informed consent form for this study must be reviewed and approved by an appropriate IRB before enrollment of participants into the study can commence.*

*It is the responsibility of the investigator to assure that all aspects of the IRB review are conducted in accordance with current Federal Regulations. A letter documenting IRB approval for the protocol must be received by the Principal Investigator before initiation of the study. Amendments to the protocol will be subject to the same requirements as the original protocol. At each annual protocol renewal, an updated report of the numbers of participants and any adverse events will be provided to the IRB.*

*After completion or termination of the study, the investigator will submit a final report with a study closure notice to the IRB. This report will include any deviations from the protocol, the number and types or participants evaluated, the number of participants who discontinued, including reasons, results of the study, adverse events, and a conclusion summarizing the results.*

***Informed Consent***

*(i.e., A signed, written informed consent will be obtained from each participant before they enter the study after they have been given verbal and written information describing the nature and duration of the study. Participants will not be screened or treated until written informed consent has been obtained. The signed informed consent form will be retained with the study records and each participant will be given a copy of the signed consent form.*

*Participant information will be protected according to the privacy regulations of the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA). Each participant will be advised that their name and/or other protected health information (PHI) will need to be supplied to the PI* (and sponsor, if applicable) *as part of the study records. A HIPAA Authorization form will accompany the participant consent form to specify the PHI being used.*

***Access of Records***

*(i.e., The investigator understands that the office and hospital records of participants entered in this study will be required to be available under the supervision of the investigator or a designated representative for inspection by the FDA and or the reviewing IRB. The study records will be contained and stored in an area of restricted access to which only the study team will have access.)*

***Retention of Data***

*(i.e., The investigator will maintain adequate and complete records for the study including participants’ CRFs (data collection forms/records), medical records, laboratory reports, informed consent forms, drug accountability records, safety reports, information regarding participants who discontinued, and any other pertinent data. All records will be maintained in a locked fireproof storage room to which only study investigators have access.*

*All records will be retained by the investigator for \_\_\_ years following the date of the approval of a drug application by the United States Food and Drug Administration (FDA) or \_\_\_\_ years after completion of the study, whichever is first. If no New Drug Application is filed, the records will be retained for 7 years following completion of the study.*

*These records will be available to copying and inspection if requested by a properly authorized employee of the Department of Health and Human Services, under the supervision of the investigator or a designated representative and in accordance with federal regulations.)*

***Deviation from the Protocol***

*(i.e., The investigator will not deviate from the protocol without obtaining written approval from the IRB. In medical emergencies, the investigator will use medical judgment and will remove the participant from immediate hazard, then notify the IRB regarding the type of emergency and course of action taken. Any other changes or deviation in the protocol will be made as an amendment to the protocol and will be approved by the IRB before being implemented.)*

***Reports***

The protocol should specify not only dissemination of results in the scientific media, but also to the community and/or the participants and consider dissemination to the policy makers where relevant. Publication policy should be clearly discussed (for example, who will take the lead in publication and who will be acknowledged in publications, etc.)

The investigator will submit accurate and adequate:

* Written progress reports to the IRB at appropriate intervals not exceeding one year
* Special reports to the IRB on any serious unexpected or life-threatening adverse event or death occurring in relationship to the study whether regarded as drug related or not and will report the event to regulatory authorities, as applicable
* Final report, including study results, to the IRB within \_\_\_\_ months after study completion or termination (study results should be shared with participants by sending a letter or having a meeting/presentation inviting participants to hear the results)

**BUDGET**

As applicable, include a brief summary of estimated expenses for this study. Include the projected funding source, if applicable. You must describe a budget for time and effort of individuals who will be involved in study conduct (i.e., PI, sub-I's, statisticians, research coordinators, information technology data personnel and health information management personnel). You must include a description of the materials needed to conduct the study and their estimated costs (paper, binders, publication costs, poster presentation costs)

**References/Bibliography**

Identify any literature cited for any information referenced in the protocol. Organize this information like that found in a medical journal.