CLINICAL PROTOCOL

TITLE: PL-208: A Multi-Center Trial of the ProLung Test™ (Transthoracic Bioconductance Measurement) as an Adjunct to CT Chest Scans for the Risk Stratification of Patients with Pulmonary Lesions Suspicious for Lung Cancer

PROTOCOL NUMBER: **PL-208**

STUDY TEST: **ProLung Test**

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DATE OF PROTOCOL: **July 2012**

AMENDMENT 2: **July 2016**

PROTOCOL SIGNATURE PAGE

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By signing below, the Investigator agrees to adhere to the protocol as outlined and agrees that any changes to the protocol must be approved by Fresh Medical Laboratories prior to implementing the change or submission of the change for approval by the Institutional Review Board (IRB).

This Study will be conducted in accordance with current appropriate local regulations, HIPAA (Health Insurance Portability and Accountability Act of 1996) requirements, FDA's good clinical practice regulations (GCPs) ISO 14155: 2011, the Declaration of Helsinki, and local ethical and legal requirements.

This study will be listed for disclosure to the extent required by law.

Investigator's Signature: _____

Printed Name: _____

Name of Institution/Company:_____

Date: _____

Medical Data Safety Monitor Signature:_____

Date:_____

Please send a signed copy of this page to Fresh Medical Laboratories via the facsimile to 801.204-9633 or email mag@prolungdx.com listed on the title page of this protocol PRIOR to submission to your institution's IRB.

Glossary

AE	Adverse Event
BIA	Bioelectrical Impedance Analysis
BP	Blood Pressure
PROLUNG	Transthoracic Bioconductance Test
CRF	Case Report Form
CT	Computed Tomography
DCF	Data Clarification Form
EKG	Electrocardiogram
FDA	Food and Drug Administration (United States)
PL	ProLung or Fresh Medical Laboratories Inc., or FML
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accounting Act
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IPL	Indeterminate Pulmonary Lesions
IRB	Institutional Review Board
NCI	National Cancer Institute
NCN	Non-calcified nodule
NSCLC	Non-Small Cell Lung Cancer
ODA	Optimal Data Analysis
Operator	Bioconductance measurement operator
PENS	Percutaneous Electrical Nerve Stimulation
PET	Positron Emission Tomography
PI	Principal Investigator
RI	Reliability Index
SAE	Serious Adverse Event
SCLC	Small Cell Lung Cancer
SDV	Source Document Verification
TENS	Transcutaneous Electrical Nerve Stimulation
UADE	Unanticipated Adverse Device Effect

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1.0 Introduction

1.1 Needed: Immediate and Accurate Risk Stratification for Lung Cancer

Lung cancer is the deadliest form of cancer, with a 5-year survival rate in the United States of 16%[i]. Currently, it is difficult to detect and diagnose lung cancer early enough for treatment to be effective. New, immediate, and non-invasive methods are needed to stratify the risk of this disease in its earliest stages. Fresh Medical Laboratories' bioconductance technology has demonstrated the potential to meet these requirements.

The current standard of care for the detection of lung cancer involves the use of CT chest scans to evaluate patients with lesions suspicious for lung cancer. While these scans provide important information about the location and size of lung lesions and raise suspicion of lung cancer, they have limited capacity to determine immediately the malignant or benign nature of the lesions they identify. In the screening setting, nearly 25% of all CT screens are "positive" for an indeterminate nodule; among these 94% of non-calcified nodules are determined to be benign.[ii] This presents a significant diagnostic challenge.[iii,iv] Given the frequency of benign disease, routine biopsy in an indeterminate lesion cannot usually be clinically justified. Because of these constraints, current guidelines[v] call for repeated CT scans over a period of months or years, in order to detect malignant growth in the detected lesion(s).

The NCI recently concluded a seminal, multi-center clinical trial in which three repeated CT screenings over a two-year period resulted in a 20.0% decrease in mortality for the high risk study cohort.[vi,vii] While these results are promising, concerns remain about repeated radiation exposure and the persistent high rate of false positives, potentially leading to extended evaluation and/or unnecessary biopsy procedures. Most importantly, by the time the lesion has grown enough to suggest malignancy, it is too late to achieve optimal treatment outcomes. In addition, there are concerns about the shortage of clinical infrastructure to manage the numbers of patients that would screen positive for cancer[viii]. The 2011 International Association for the Study of Lung Cancer Core Task Force and Screening Implementation Group[ix] recommended the development of new technologies to stratify the risk of cancer patients with indeterminate pulmonary nodules. A fast, accurate and non-invasive technology that could immediately stratify the risk of lung cancer in patients with an indeterminate pulmonary lesion could provide invaluable life-saving clinical information as well as reduce prolonged anxiety and unnecessary procedures in patients with indeterminate lesions.

1.2 Fresh Medical Laboratories ProLung Test™

Fresh Medical Laboratories transthoracic bioconductance technology (ProLung Test™) has demonstrated the ability to differentiate patients with indeterminate lung lesions as seen by CT[x]. The value of this innovation lies in its potential to efficiently stratify the risk of lung cancer in a non-invasive, non-radiating test that provides immediate results. The Fresh Medical Laboratories ProLung Test has been determined to be non-significant risk by previous IRBs. To date, 160 patients have been evaluated for safety; all completed the entire measurement session and none discontinued measurement due to discomfort or an adverse event[xi].

2.0 Study Objectives

2.1 Objectives and Aims

The primary Study hypothesis is that the ProLung Test will demonstrate safety and efficacy in the risk stratification of patients with pulmonary lesions identified by CT that are suspicious for lung cancer. A statistically significant result will indicate that patients with a high ProLung Test result have a greater risk of developing lung cancer than patients with a low test result.

There are three Specific Aims of this study:

1. Optimize and confirm the stability of the ProLung Test risk-stratification algorithm in patients with a diagnosis.
2. Externally validate the efficacy of the ProLung Test risk-stratification algorithm by comparing the test result to the conclusive patient diagnosis.
3. Assess the safety and tolerability of the ProLung Test procedures.

3.0 Study Design

This Study consists of two distinct phases, Stabilization and Validation. The Study will collect data from multiple sites (3 to 20), and each site may enroll patients and collect data for the Stabilization and Validation Phases with a minimum of three sites for the Validation Phase. In this multi-center Study, the patient's known diagnosis (of either a malignant or benign outcome) will be compared to the ProLung Test results. The patient's diagnosis is determined by tissue biopsy, surgical resection or by CT follow-up detecting significant nodule growth during a 1 year time frame. This Study follows the National Comprehensive Cancer Network definition for nodule growth. Nodule growth is defined as: 1) for nodules 15 mm or smaller: an increase in mean diameter of 2 mm or more in any nodule or in the solid portion of a part-solid nodule when compared with the baseline scan, or 2) for nodules 15 mm or more: an increase of 15% in mean diameter when compared with the baseline scan. Mean diameter is the mean of the longest diameter of the nodule and its perpendicular diameter[xii]. If no significant growth is detected and the nodule is not definitively diagnosed by biopsy or surgical excision, the outcome will be considered benign unless indicated otherwise in the patient's medical record.

3.1 Stabilization Phase

The objective of the Stabilization Phase is to optimize and confirm the stability of the ProLung Test risk-stratification algorithm in patients with a diagnosis (Specific Aim 1). In this open multi-center Study, the patient's known diagnosis (of either a malignant or benign outcome) will be compared with the Algorithm. Certain components of the Algorithm may be adjusted or optimized to improve overall performance of the ProLung Test in the Study population.

Initially, 100 patients will be enrolled into the initial cohort of the Stabilization Phase. If required by the Sponsor, up to an additional 100 patients, in groups of 25 patients, may be enrolled in the Stabilization Phase until the Algorithm achieves stability as determined by the Sponsor. Once Algorithm stability has been determined and confirmed by the Sponsor, the risk stratification Algorithm will be locked for the

Validation Phase. Data from the Stabilization Phase will also be utilized to assess the safety and tolerability of the ProLung Test procedures.

3.2 Validation Phase

The objective of the Validation Phase is to externally validate the efficacy of the ProLung Test risk-stratification Algorithm by comparing the test result to the conclusive patient diagnosis (Specific Aim 2). The risk stratification Algorithm result is recorded and locked for this Phase.

The Validation Phase is blinded as follows:

> Sponsor's Statistician is blinded from the patient's diagnosis outcome (malignant, benign or inconclusive). The patient's ProLung Test results will be provided to the Sponsor and/or Statistician.
>
> Site clinical study team, including the PI, study coordinators, and ProLung Test operators, is blinded from the ProLung Test risk stratification algorithm results. At each site, the patients' diagnoses are accessible by the site clinical study team.

Initial Study enrollment in the Validation Phase will be 100 patients. To maintain the Study's statistical power, enrollment will continue until there is both a minimum of 100 subjects and a minimum of 40 ProLung high risk and a minimum of 40 ProLung low risk subjects are enrolled. If required by the Sponsor and/or Statistician, up to an additional 50 patients, in groups of 25 patients, may be enrolled in the Validation Phase prior to breaking the statistical blind. The statistical blind is broken at the end of Study recruitment and monitoring with approval by the Sponsor and/or Statistician.

If required by the Sponsor and/or Statistician, up to an additional 35 subjects may be enrolled in either the Stabilization or Validation Phase to replace the enrolled subjects that were lost to follow-up or fail the Study Inclusion / Exclusion Criteria.

3.3 Safety and Tolerability

To assess the safety and tolerability of the ProLung Test procedures, the Study will utilize the data from all patients enrolled in the Stabilization and Validation Phases. Information collected about adverse events and tolerability will be analyzed as described in sections 5.8 and 6.0 (Additional Data Collection and Adverse Events).

3.4 Study Sample Size

This Study may enroll a maximum of 200 in the Stabilization Phase and 150 in the Validation Phase. The Study may enroll a minimum of 100 in the Stabilization Phase and 100 in the Validation Phase. In the Validation Phase, the sample size has been determined to provide greater than 90% power to reject the primary study hypothesis.

3.5 Assignment to Study Phase

The site study teams will enroll patients sequentially into the Stabilization Phase. When the Sponsor has confirmed the stability of the ProLung Test risk-stratification Algorithm, the Stability Phase will be completed and the Validation Phase launch will be confirmed by written notice to each site clinical study team. Prior to enrollment in the Validation Phase, Study blinding will be established and monitored.

3.6 Monitoring

The study Sponsor will provide monitors to monitor Protocol compliance and provide guidance pertaining to the management of the Study.

3.7 Study Design Summary

Design Element	Stabilization Phase	Validation Phase
Patient Enrollment	100-200 patients	100-150 patients
Sites	3-20	3-20
Blinding and Breaking the Statistical Blind	Open phase - Optimize algorithm with known diagnosis	Blinded phase – Sponsor's Statistician is blinded to diagnosis and site study team is blinded to ProLung Test results. The statistical blind is broken at the end of Study recruitment and monitoring with approval by the Sponsor and/or Statistician.
Primary Objectives:	Stability of ProLung Test risk stratification algorithm as confirmed by Sponsor.	Clinical efficacy in the risk stratification of patients with indeterminate lesions.
	Safety and tolerability	Safety and tolerability

4.0 Subject Selection and Participation

4.1 Inclusion Criteria

Subjects who meet <u>all</u> of the following criteria may be enrolled in this Study:

1. Subject is male or female, age 18 or older.
2. Subject has undergone CT scan of the lung(s) that indicates one or more nodules or lesions suspicious for lung cancer.
3. Subject's pulmonary nodule or lesion is greater than 4mm. Size is determined by the largest nodule or lesion dimension identified from CT imaging.
4. Subject meets one or more of the following conditions:
    - indicated for a tissue biopsy

- indicated for surgical resection of the lung

5. Subject must be able to receive a ProLung Test
   - within 60 days of abnormal CT (*Inclusion Criterion 2 & 3*)
   - within 60 days prior to the tissue biopsy or surgical resection (*Inclusion Criterion 4*).
6. Subject is capable of understanding and agreeing to fulfill the requirements of this Protocol.
7. Subject has signed the IRB/IEC approved Informed Consent Form ("ICF").

4.2 Exclusion Criteria

The following criteria will disqualify a subject from enrollment into this Study:

1. Subject has an implanted electronic device in the chest.
2. Subject receiving therapy for suspected chest infection such as fungal infection or tuberculosis.
3. Subject with diagnosed malignancy other than lung cancer, non-melanoma skin cancer or any cancer in which the Principal Investigator does not suspect metastatic disease to the lung, who has 2 or more suspicious pulmonary nodules.
4. Subject has received an invasive medical or surgical procedure within the thoracic cavity within 30 days prior to the ProLung Test or within the previous 14 days for a bronchoscopic procedure.
5. Subject presents with an anomalous physical or anatomical condition that precludes ProLung Test measurement.
6. Subject will have undergone unusually strenuous exercise within 24 hours.
7. Subject who has significant systemic diseases such as uncontrolled diabetes, advanced heart failure, or a recent myocardial infarction, or other medical condition such as severe morbid obesity that in the judgment of the Principal Investigator would make him/her unsuitable for the Study.

4.3 Subject Discontinuation

In accordance with the Declaration of Helsinki, subjects are free to discontinue the Study at any time for any or for no reason. Should a subject decide to withdraw, every effort should be made to obtain information about the reason(s) for discontinuation. The Principal Investigator also has the right to withdraw subjects from the Study at any time at his/her discretion.

4.3.1 Events Necessitating Premature Discontinuation

The occurrence of any one of the following events may necessitate premature discontinuation of a subject from the Study:

- Subject develops any of the exclusion criteria after enrollment.
- Subject is unwilling to continue in the Study.
- Subject does not comply with the Study Protocol.
- Subject being followed by CT for nodule growth who does not receive a follow-up CT by their 1-year enrollment anniversary or within 60 days after their 1-year enrollment anniversary.

- Principal Investigator decision.

4.3.2 Events Eliminating Subjects from Primary Analyses

- Incomplete or lost medical records.
- Inconclusive biopsy result.
- Incomplete ProLung Test data.

5.0 Study Procedures

5.1 Study Procedures Summary

Patient Visit:

- Obtain demographics
- Obtain smoking history, and details of industrial exposure
- Obtain recent medical and surgical history
- Record concomitant medications (most recent 2 weeks)
- Conduct physical examination
- Perform ProLung Test. Adverse Event assessment
- Administer Tolerability Questionnaire
- Print out ProLung Test summary report for inclusion in patient's source documentation

Patient Data and Source Documentation Collection:

- Transmit patient data to Sponsor weekly as patients complete ProLung Testing
- Obtain radiological reports including CT, chest x-ray, follow-up CT, PET, and MRI.
- Obtain surgical report
- Obtain biopsy report
- Obtain pathology report

5.2 Informed Consent

The Informed Consent must be documented on the current IRB-approved version of the informed consent form. The consent process must also be documented in the site's Study Notebook. The Informed Consent must be obtained prior to performing any Study-specific procedures. The patient must be given a fully executed copy of the informed consent form. The site retains the original signed informed consent form.

5.3 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria must be evaluated prior to subject enrollment and at the start of the ProLung Test protocol. Documentation that the subject meets all of the inclusion criteria and none of the exclusion criteria must be present in the subject's source documents in Site Study Notebook. If an exemption to the inclusion or exclusion criteria is granted by the Sponsor, such exemption will be recorded in the CRF.

5.4 Demographics and Relevant Health History

a. The subject's gender, age, and ethnicity (patient's optional response) will be recorded.

b. The subjects will be asked about their smoking history including pack-years smoking and how recently they discontinued smoking if applicable.

c. The subjects will be asked about their past and current exposure to cancer-causing agents.

d. The subjects will be asked about their current pulmonary symptoms.

e. A brief medical and surgical history will be obtained. The medical history should include all significant current conditions, including recent illnesses and history, within two years of the time of the ProLung Test. The surgical history will include any major surgeries performed within five years of the date the ProLung Test is performed.

5.5 Physical Exam

A physical examination will be performed at the patient visit to assess the patient's general physical status. Physical characteristics of height, weight will be measured and recorded.

5.6 Concomitant Medication Assessment

The subject's usage of concomitant medications within the most recent 2 weeks will be recorded including name of the drug, dosage, and reason for use. Medications will include both prescription and over-the counter drugs, but will EXCLUDE herbal or nutritional supplements.

5.7 ProLung Testing Session

The ProLung Test operator non-invasively measures certain anatomical locations on the surface of the skin. ProLung Test locations are displayed immediately prior to measurement and sequenced for the Operator performing the test. Real-time assessment of the quality of each measurement assists the operator to capture measurement data.

All operators involved in measuring subjects will have previously been trained and certified in use of the ProLung unit as provided by the Sponsor and described in detail in the Operator Training Manual. They will demonstrate competence based on criteria established by the Sponsor prior to using the ProLung Test on enrolled patients. The ProLung Test requires an average of 20 minutes. In previous clinical studies, time required to complete the ProLung Test ranged from 16 to 23 minutes.

Patient ProLung measurement data will be printed out at the end of each test session and placed into the subject's source document file. This print-out only contains summary information of the collected data and does not represent a complete data-file that is analyzed with the Algorithm. Weekly, ProLung Test data will also be stored to a Sponsor provided USB flash drive which is used to send ProLung Test data to the Sponsor through a secure Study file sharing website.

5.8 Additional Data Collection

<u>Post-Measurement (following ProLung Test)</u>

- Adverse Event assessment

- Tolerability Questionnaire: Following the ProLung Test, subjects will be asked to complete a brief questionnaire regarding their experience and perception of the procedure. The questions are:

    1. Did the test cause any discomfort? If so, please describe.

    2. Did the time required for measurement seem too long? If so, what amount of time seems reasonable?

    3. Would you agree to undergo measurement again? If not, what is the reason?

    4. Do you have any suggestions for improving the measurement procedure? If so, please describe.

5.9 End of Study

The subject's active participation in the Study is completed once the ProLung Test and the adverse event assessment have been completed. The subject's active participation concludes prior to the performance of the lung biopsy.

5.10 Follow-up Outcome Assessment

The outcomes of any ancillary diagnostic procedures conducted as part of normal clinical care will be collected for further analysis and the provided CRF page(s) will be completed as appropriate. The Study participant will sign a "Release of Medical Information" at the time of the consent process. All laboratory and radiological tests performed to further evaluate the abnormal chest CT will be obtained by the study team and kept as part of the participant's source document. This will include but are not limited to results of biopsies, sputum cytology, repeat chest CT scans, repeat chest radiography, MRI and PET scans.

Prior to the close of the Study, each site will obtain the most recent CT Report and History and Physical (if available) for all enrolled subjects who received a benign biopsy result or a CT follow-up showing stability to re-confirm that the subjects have remained free of malignancy.

5.11 Adverse Event Assessment

During, and immediately following the ProLung Test, subjects will be observed for any potential adverse event. Any unanticipated and unfavorable sign, e.g., a symptom described by the patient or noted by the site staff will be recorded as an adverse event in the source documents and CRF, and followed-up with more specific questions or actions as required.

6.0 Adverse Events

6.1 Adverse Event

6.1.1 Adverse Event Definition

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject involved in the testing of a medical device and which does not necessarily have to have a causal relationship with the device.

An adverse event can therefore be any unanticipated and unfavorable sign, symptom or disease temporally associated with the use of a device, whether or not considered related to the product.

An AE includes:

- An exacerbation of a pre-existing illness or symptom
- Post-measurement (i.e. after the ProLung Test) events that occur as a result of protocol-mandated procedures
- A condition detected or diagnosed after device utilization

An AE does not include:

- The disease or disorder being studied or signs and symptoms associated with the disease/disorder unless there is an unexpected worsening of the subject's condition
- A pre-existing disease or condition present at the start of the Study that did not worsen
- Elective medical or surgical procedures unless resulting from a SAE

6.1.2 Procedures for Adverse Event Reporting

Adverse events will be recorded from the time the subject has begun measurement with the device through Study completion. Any change in medical status or untoward event that occurs from the time the subject signs informed consent and undergoes ProLung measurement will be recorded as a baseline condition in the medical history.

Any unanticipated and unfavorable sign (e.g., a symptom or physical anomaly described by the subject or noted by the site staff) will be recorded as an adverse event. Changes in the subject's physical or mental condition or other responses must be reported as AEs if they are considered clinically significant by the Principal Investigator, if they fulfill SAE criteria or if they cause discontinuation from the Study.

AEs not resolved at the end of the ProLung Test will be followed after clinical Study completion or as long as medically relevant as judged by the Principal Investigator.

The Sponsor will conduct an evaluation of any unanticipated adverse device effect (UADE) in accordance with local regulations and report the results of the evaluation to the Investigator, IRB and any necessary authorities within 10 working days after the Sponsor first receives notice of such an event.

6.2 Serious Adverse Event

6.2.1 Serious Adverse Event Definition

An adverse event is considered serious if it:

- Occurs during Study measurement (ProLung Test) or immediately thereafter and,
- Meets any of the criteria outlined in the following section

An SAE is any adverse event that results in any of the following outcomes:

- Death or is life-threatening: A life-threatening SAE is any SAE that places the subject in the opinion of the Principal Investigator, at immediate risk of death from the reaction as it occurred. It does not include a reaction that, had it occurred in a more serious form, might have caused death
- Persistent or significant disability/incapacity
- Inpatient hospitalization or prolongation of existing hospitalization

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the subject, and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Scheduled and/or elective hospitalizations will not be defined as serious adverse events for this clinical Study.

6.2.2 Procedures for Serious Adverse Event Reporting

The Principal Investigator must inform the Sponsor and the Medical Monitor within 24 hours of becoming aware of any SAE that occurs during the course of the clinical Study. The Principal Investigator may communicate the event to the Sponsor or Medical Monitor; however, a completed SAE form must be faxed or scanned and emailed to the Medical Monitor and to the Sponsor within 24 hours of the initial reporting. All serious events must be reported, whether or not they are considered causally related to the device utilization. Appropriate clinical, diagnostic, and laboratory measures must be performed to delineate the cause of the SAE in question and the results reported. All tests that reveal an abnormality that is considered device related should be repeated at appropriate intervals until:

- The cause is determined
- A return to baseline value occurs
- Stable results are obtained over 2 to 3 consecutive readings that are clinically acceptable and safe for the subject

The Principal Investigator is required to assess the causal relationship to the Study device for each SAE to determine if the event is associated with the use of the device. Events should be classified as associated with the use of the device if there is a reasonable probability that the experience may have been caused by the device.

The Sponsor will conduct an evaluation of any UADEs in accordance with 21 CFR 812.46(b) and report the results of the evaluation to the Investigator, IRB and FDA within 10 working days after the Sponsor first receives notice of the effect in accordance with 21 CFR 812.150(b(1)). The Sponsor will terminate the investigation when a determination has been made that an unanticipated adverse device effect presents

an unreasonable risk to subjects. Termination will occur no later than 5 working days after the Sponsor makes the determination and not later than 15 working days after the sponsor first received notice of the effect in accordance with 21 CFR 812.46(b)(2).

7.0 Data Management

7.1 Data Collection

The site study team will make data entry on the case report forms (CRF)s and keep records of the subject's visit in the source documents for that site. The Principal Investigator or designee will be responsible for the timely recording of patient data.

To ensure that correct data have been entered on the CRF, CRFs will be 100% source-data verified by a Monitor from the Sponsor, who will notify the Principal Investigator or designee regarding questions or missing data. When data have been entered in the CRF, signed by the Principal Investigator, and all questions and/or corrections have been resolved and verified, the original of each CRF page(s) will be collected by the Sponsor. The PI will retain a copy of completed and monitored CRF pages. Any remaining questions or missing data subsequent to retrieval of a CRF page from a site will be noted on Data Clarification Forms (DCFs), which will be sent to the Principal Investigator. DCFs should be completed by the Study site and signed by the Principal Investigator in a timely manner.

ProLung Test subject data will be sent to the Sponsor on a weekly basis as subjects are enrolled.

7.2 Record Retention

All records relating to the conduct of the Study are to be kept in a locked and secure location and held by the Principal Investigator until notified by the Sponsor that the records may be destroyed. Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region 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, however, if required by the applicable regulatory requirements or by agreement with the Sponsor. The Sponsor will notify the Principal Investigator of the retention period required to satisfy appropriate regulations. If the Sponsor has not notified the Principle Investigator and 10 years has passed since the last subject was enrolled, all records may be destroyed.

The Principal Investigator will allow representatives of the Sponsor's monitoring team and of the appropriate regulatory authority to inspect all Study records, CRFs, and corresponding portions of the Study patients' office and/or hospital medical records at regular intervals throughout the Study and after the Study has completed if required. These inspections are for the purpose of verifying adherence to the protocol, the completeness and exactness of the data being entered in the report forms, and compliance with regulations.

8.0 Study Analyses

8.1 Statistical Analysis Plan

Stabilization Phase

Stabilization Phase is not blinded. The malignancy or benignity status of the patients will be available as described in Section 4.0 Study Design. Algorithm stabilization will be tested by the Sponsor against prior clinical results and across study patients. In addition, in this phase, the Sponsor and Statistician may evaluate the impact of demographic, geographic and anatomical factors on the stability of the risk stratification Algorithm. Certain inter and intra patient bioconductance factors may also be evaluated for impact on Algorithm stability.

The statistical approach to the risk stratification Algorithm stabilization will be to modify the Algorithm using Optimal Data Analysis (ODA) programmed in Stata™ version 11 statistical software that allows a large number of variables at a time while treating each measurement variable independently. This will be in contrast to traditional multivariable regression that treats variables as possibly correlated, but only allows for a small number of predictor variables at a time which will also be used to optimize the Algorithm. Variable selection, cut-point determination, decision nodes, and so on, will be based on variables that provide improved discrimination and validate successfully.

After stability of the risk stratification has been confirmed by the Sponsor, the Algorithm will be locked, and further changes will not be permitted.

Validation Phase

The locked risk stratification Algorithm will be applied to the patients participating in the Validation Phase in which the Sponsor's Statistician is blinded to the actual patient diagnosis.

With respect to determining the optimal sample size of the Validation Phase, it is assumed that the sensitivity of the ProLung test (probability of having had a high risk test among subjects who subsequently had a malignant biopsy) is 70% and that the specificity (probability of having had a low risk test among subjects who subsequently had a benign biopsy) is also 70%. It is further assumed that among the patient population studied in this Study, approximately 70% will have a malignant biopsy. Based on these assumptions, 88 subjects will provide 90% power to reject the primary null hypothesis. The primary analysis will only include subjects who have a biopsy within 60 days of their ProLung test and have a definitive biopsy result. Subjects who fail to have a biopsy or do not have a definitive biopsy result will be excluded. To account for as many as 12% of such subjects, 100 subjects will be enrolled into the Validation Phase. Furthermore, to maintain the Study's statistical power, enrollment will continue until there is both a minimum of 100 subjects and a minimum of 40 ProLung high risk and a minimum of 40 ProLung low risk subjects are enrolled.

The primary null hypothesis is that the relative risk of a malignant biopsy among subjects with a high risk ProLung test result to that of subjects with a low risk ProLung test result is 1.0, vs. the alternative hypothesis that the relative risk is different from 1.0. This hypothesis will be tested by a two-sided Fisher's Exact Test at the 5% level of significance. If the relative risk is found to be greater than 1.0

($p<0.05$), it will be concluded that subjects with a high risk ProLung test result are prognostically at greater risk to have a malignant biopsy than subjects with a low risk ProLung Test result. The relative risk will also be presented with its approximate 95% confidence interval.

8.2 Safety/Tolerability Analyses

Subject data on AEs and SAEs will be collected during and immediately following the ProLung Test period. Treatment emergent AEs will be summarized using descriptive statistics (e.g., number and percentage of patients). Treatment emergent AEs are defined as AEs whose onset occurs, severity worsened or intensity increases after undergoing the ProLung Test. We will survey the subjects for their comfort and tolerance of the overall test procedure.

8.3 Baseline and Demographic Data

Patient information including age, gender, smoking history, occupational exposure, and ethnic background (when available) will be collected and used to summarize the baseline and demographic characteristics for each Cohort and overall.

9.0 Administrative and Ethical Requirements

9.1 Declaration of Helsinki and Ethical Review

The Study will be performed in accordance with the principles stated in the Declaration of Helsinki, FDA GCP regulations and ISO 14155: 2011 requirements. The final Study protocol, including the final version of the Informed Consent Form (ICF) to be used, must be approved by an IRB before enrollment of any patients in the Study. The opinion of the IRB will be dated and given in writing. A list of those present at the committee meeting (names and positions) should be attached. The regulatory authority and/or IRB will be informed of any SAEs and amendments to the protocol according to local and FDA requirements. All correspondence with the IRB must be filed by the Principal Investigator and a copy forwarded to the Sponsor.

9.2 Monitoring Procedures and Auditing of Data

A Study Monitor will review the Study data during, and at the end, of the investigation. All personnel involved in the Study should be prepared to make time to discuss the data with the Monitor.

The following will be reviewed by the Study Monitor:

- Subject enrollment
- Compliance with the protocol
- Informed consent verification
- Completion of the CRFs and the correction of any missing or incorrect data
- 100% Source document verification (SDV)
- Adverse event identification and reporting

- Contents of the Investigator File and Study Documents

In accordance with Good Clinical Practices (GCP), the Monitor will undertake auditing of data recorded on the CRF against the source documents. The purpose of source document verification is to verify, so far as is possible, that the information on the CRF reflects the data recorded in the patient's hospital/clinic chart. SDV will be performed with due regard for subject confidentiality and in accordance with local privacy regulations, and HIPAA requirements if any.

9.3 Subject Information and Consent

The Principal Investigator or designee will ensure that the subject is given full and adequate verbal and written information about the nature, purpose, possible risks and benefits of the Study. Subjects must also be notified that they are free to stop participating in the Study at any time without prejudice to the quality or level of care provided. Subjects will be informed that the effects of the device will be followed throughout the Study. The subject should be given the opportunity to ask questions and time to consider their participation. The Principal Investigator or designee is responsible for obtaining and documenting written informed consent from all subjects before enrollment. The subject must be given a copy of the fully executed ICF. The Principal Investigator must retain an original fully executed ICF.

9.4 Subject Data Protection

All data provided to the Sponsor will be identified by a unique subject number, thereby ensuring that the subject's identity remains unknown. The subjects should be informed in writing, that their data may be stored and analyzed in a computer, with confidentiality maintained in accordance with local regulation.

The subjects should also be informed in writing that authorized representatives of the Sponsor and/or regulatory authorities may require access to those parts of the chart records relevant to the Study, including medical history, for data verification.

The Principal Investigator is responsible for keeping a subject identification list of all subjects screened and enrolled which includes the following information: subject number, full name, and a secondary unique identifier (i.e., hospital/clinic number).

9.5 Financial Disclosure

All investigators participating in clinical studies must comply with local and national financial disclosure regulations if applicable. If required, these are to be submitted in support of an application for market approval.

The financial information typically disclosed includes four types of data. They are:

i) significant equity interest in the Sponsor held by the Investigator equal to or exceeding US $50,000

ii) any financial arrangement entered into between the Sponsor and the investigator whereby the value of the compensation to the investigator for conducting the Study could be influenced by the outcome of the Study

iii) compensation, other than that which is associated with conducting the referenced Study, paid by the sponsoring company to an investigator, exclusive of the costs of conducting the clinical Study or other sponsored clinical studies (e.g., a grant to fund ongoing research, compensation in the form of equipment or retainers for consultation or honoraria, etc.)

iv) proprietary interest in the product tested in the covered Study held by an investigator.

To comply with this regulation, investigators are required to complete the financial disclosure form which will be supplied at site initiation. These disclosure requirements cover Principal Investigators, co-investigators and sub-investigators and their spouses and dependent children. The originals of these documents must be included in the Principal Investigator's regulatory documents.

9.6 Changes to the Protocol

No change in the Study procedures shall be effected without the mutual agreement of the Sponsor and the Principal Investigator. All changes must be documented as signed protocol amendments, or as a revised protocol. Changes to the protocol require notification to or approval by the IRB and the regulatory authorities before implementation. Local regulatory requirements must be followed.

The Sponsor is responsible for the distribution of protocol amendment(s) to the Principal Investigator(s) and those concerned within the conduct of the Study. The Principal Investigator is responsible for the distribution of all amendments to the IRB and all staff concerned at his/her center.

Appendix I: Background Information

1.0 Scientific Literature

Bioelectrical Properties of Living Tissue

By definition, electrical impedance is the ratio of the voltage difference to the current across a circuit or a body (Ohm's law), and conductance is the inverse of impedance (1/impedance). The dielectric properties of human cells and tissue are widely recognized and are essential for several diagnostic procedures currently in use, such as the electrocardiogram.[xiii] Bioelectrical conductance is the basis for the monitoring of certain physiological processes such as "impedance plethysmography" for measuring blood volume or Electrical Impedance Tomography" (EIT) for assessing lung ventilation[xiv] [xv]. Other examples include multi-frequency Bioelectrical Impedance Analysis (BIA) to measure the electrophysiological properties of cell membranes and related body tissues as a predictor of body weight, fat content, and extracellular and intracellular water in a wide range of medical conditions.[xvi]

Bioconductance and Malignant Tissue

Several experimental studies have demonstrated that the electrical properties of cancerous tumors vary significantly from normal, nonmalignant tissue[xvii]. The mechanism has been attributed to the high water and sodium content within cancerous tissues with movement of potassium, magnesium and calcium out of the cell[xviii,xix]. Other possible contributors include not only altered membrane permeability but also changes in membrane composition, the nucleus to cytoplasm ratio as well as alterations in cellular composition and density[xx] [xxi]. Many of the published studies are in breast cancer. For example, one study examined a set of 120 *impedivity spectra* collected in breast tissue immediately after excision from 64 patients undergoing breast surgery[xxii]. This investigation reported that no significant differences were found between groups of normal breast tissue and those consisting of benign pathology such as fibroadenomas. However, the bioelectrical properties of the carcinoma group differed from the normal and benign tissue groups[xxiii]. *In vitro,* hepatic studies have found differential electrical conductivity changes between tumor and control tissue in a rat model[xxiv]. Another *in vitro* study examined brain, breast, gastric and colon cancers that had been implanted in a nude mouse model, grown, and then excised for investigation of electrical conductance properties[xxv]. This investigation found that all four cancerous tissues had conductance values that were clearly different from non-cancerous tissue[xxvi].

In summary, studies conducted at the cellular and tissue level (as well as on recently excised human tissue) have demonstrated differences in electrical conductivity associated with various disease states including cancer.

Bioconductance and Cancer Diagnosis

Many clinical investigations have examined the potential of using electrical properties to aid in cancer diagnosis. Electrical bio-conductance has been shown to successfully discriminate between cancerous and non-cancerous tissue for skin cancer,[xxvii] cancer of the lymph nodes[xxviii] and breast cancer [xxix] and has shown promise as a screening tool for the detection of cervical[xxx] and colorectal cancers[xxxi].

There is also growing evidence regarding differences in lung tissue bioconductivity associated with lung cancer.[xxxii] In one non-invasive study of bioconductance measurement in lung cancer, bioelectric impedance vector analysis in patients with known advanced stage (IIIB and IV) lung cancer (66) was compared with healthy controls (56)[xxxiii]. The conclusion drawn by Toso and colleagues is that a distinct difference in transcutaneous bioimpedence (a combination of resistance and capacitance) can be seen between patients with advanced lung cancer and normal controls, and that in the advanced cancer cohort, regardless of their measured Body Mass Index (or BMI, one commonly used index of nutrition), bioconductance measurement differences provided a better measurement of survival, and hence prognosis.

A second study utilized electrical impedance tomography to provide *in vivo* imaging prior to surgery in 22 patients with single sided lung cancer and 7 healthy subjects[xxxiv]. These investigators found that "images" in 19 of the 22 affected lung cancer patients showed differences in conductivity that were statistically different from the average conductivity of a healthy lung.

In addition to these studies, the ProLung Test developed by Fresh Medical Laboratories has been examined in 3 clinical studies, which evaluated the feasibility of using a non-invasive bioconductance test to discriminate between malignant and non-malignant lung tissue.

2.0 Clinical Studies: ProLung Test

The initial feasibility study, FML-201, tested the ProLung Test to discriminate between the bioconductance measurements recorded for age-and gender-matched subjects with and without biopsy-confirmed lung cancer. The second study, FML-203, examined measurement reliability and reproducibility in a normal subject sample. The third, FML -204, tested the ProLung Test's discriminatory ability in undiagnosed patients who exhibited lesions that were suspicious for lung cancer.

A. Feasibility Study (FML-201). McHenry IL 2007. The study's first Specific Aim was to investigate ProLung Test effectiveness in discriminating between clinically symptomatic patients (n=18) with and without (n=18) lung cancer. The subjects were also evaluated for any adverse events connected with use of the test.

The study was a single-site, single-blind (i.e., ProLung Test operator and statistician were unaware of subject diagnosis), two-arm design with screening and bioelectrical conductance measurement visits. Biopsy was performed prior to conductivity measurement. Figure 1 below illustrates the performance of the optimal algorithm in this initial set of patients.

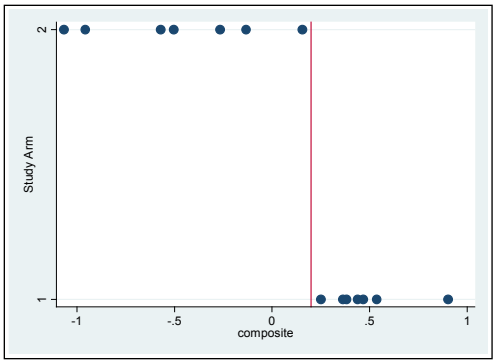

Figure 1. **Discrimination of cancer from non-cancer patients.**

Results. In the FML-201, the derived Algorithm was able to perfectly discriminate (vertical line) biopsy-confirmed cancer subjects from age- and gender-matched cancer-free subjects. X-axis: composite score units. Y-axis: study arm 1, non-cancer; study arm 2, cancer.

Conclusion. These data supported the hypothesis that trans-thoracic conductance measurements obtained using the ProLung Test distinguish statistically significant conductivity differences between cancerous and non-cancerous lung tissue in a small patient sample. This suggested feasibility of the technology. Further algorithm development with validation was planned for a subsequent larger study.

B. Reliability and Reproduceability Study (FML-203). The variability of repeated ProLung conductance measurements was investigated using a single ProLung unit and operator on 22 normal subjects over two days of testing at the Salt Lake Community College in Salt Lake City Utah. The Specific Aim was to investigate ProLung unit variability as estimated from repeated measurements on the same subject in succession.

Results. The maximum and minimum conductance results were comparable, with slightly lower standard deviations for maximum conductance readings and extremely high reliability indices for both measures. For both data sets, the same measurement points were found to have minimal variability (and maximal reliability) indices.

Conclusion. The results suggest a high degree of consistency in the ProLung measurements and support the reliability of this procedure as an adjunct to other methods used to risk-stratify patients who have suspicious lung lesions.

C. Transcutaneous Computed Bioconductance Measurement in Lung Cancer: A Treatment Enabling Technology Useful for Adjunctive Risk Stratification in the Evaulation of Suspicous Pulmonary Lesions

Methods.. The research was conducted at Johns Hopkins School of Medicine, by members of the faculty at that institution and the University of Utah School of Medicine, as well as members of the Fresh Medical Laboratories clinical staff. The Study was published in the April 2012 edition of the Journal of Thoracic Oncology. The purpose of this Study was to further develop a mathematical algorithm that discriminates between benign and malignant pulmonary lesions found on spiral chest CT scans, using the noninvasive transcutaneous computed bioconductance (ProLung) measurement Test. The Study's hypotheses were (1) designed to assess the stability of the ProLung Test classification Algorithm when used as an adjunct

to CT scan, and (2) to assess whether there are any potential safety concerns of the ProLung Test when used to evaluate patients with a positive CT scan.

Subjects age 18 and above were recruited sequentially and randomly from those who were eligible and agreed to participate in the study, and were enrolled under an IRB-approved protocol (IRB # NA_00007789). All subjects presented with one or more suspicious radiological and/or clinical finding(s) for lung cancer, and all had undergone a CT scan of the lungs that indicated one or more non-calcified nodules (NCN) or lung masses suspicious for lung cancer, or the subjects were scheduled to receive a CT scan of the lung within 14 days of enrollment.

Forty-one patients were qualified to participate in the study. The statistical approach used an optimal cut-point methodology for classifying the two patient groups (malignant or non-malignant) based on the variables associated with the conductance measurements. The cut-point that provides the best test characteristics was considered the optimal cut-point.[72]

Results: (Yung, 2012)[xxxv] [xxxvi] [xxxvii]. Using this methodology for analyzing the ProLung's bioconductance test data for the 41 patients resulted in the scatter plot in Figure 2. As shown here, 11 of the 12 patients with benign lesions had composite scores that fell below the cut-point. For the malignant cases, 26 of the 29 had composite scores above the predetermined cut-off point with 3 falling below it. Computed bio-conductance measurements discriminated between malignant lesions (29 primary lung cancers) and benign pathology (12) across a range of IPL sizes (0.8 cm and greater) with a sensitivity of 89.7% (positive predictive value 96.3%) and specificity of 91.7% (negative predictive value 78.5%).

Conclusion. This study found different bioconductance properties between cancerous and non-cancerous lung lesions and provides encouraging results for continued development of the ProLung Test.

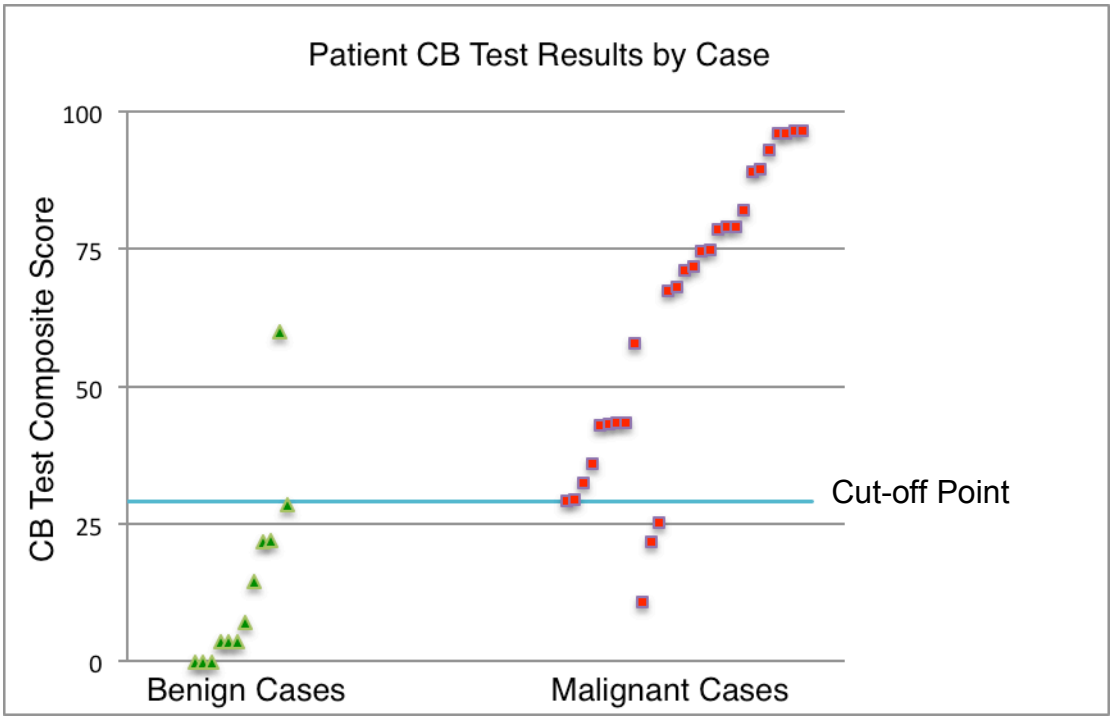

Figure 2: Patient Bioconductance (ProLung) Test Results illustrate the composite scores for the benign patients (represented by the closed triangles) and the composite scores for the malignant cases (represented by the open squares) with reference to the Cutoff Point.

3.0 ProLung Unit: Technical Description

The ProLung unit measures bioelectrical conductivity at multiple points on the skin's surface. The probe introduces a low electrical current (too low to be felt) into the body and has adhesive electrodes that measure the current at other parts of the body. The ProLung unit is shown below in Figure 3 and has three functional components as illustrated in the schematic in Figure 4. The Measurement component includes both the hardware and software that obtain and record accurate and reproducible bioelectrical conductance measurements (data sets) of the thoracic cavity, referred to as the computerized bioconductance (ProLung) test output. All of the software, hardware and unit configurations provided to the investigatory team, as illustrated below, are proprietary to the Sponsor.

Figure 3. Fresh Medical Laboratories ProLung unit with probe (on left) and associated computer screen (on right) illustrating the Operator display.

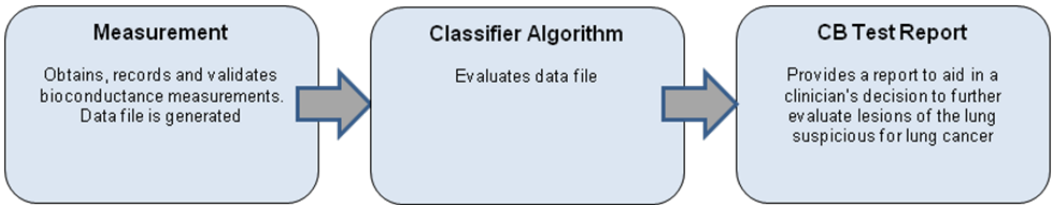

Figure 4. ProLung Functional Components shown as a flow chart illustrating the sequence of function of the ProLung unit.

3.1 Classifier Algorithm Design and Function

With reference to Figure 4, above, following measurement, the characteristics of each subject's data set are recorded and validated. A ProLung data set or file consists of the measurements obtained at the

acquisition points for each subject. The classifier Algorithm then analyzes the data set. The algorithm processes specific properties of the data set to generate a report to aid the clinician in assessing the risk of malignancy associated with known lesions.

3.2 Classification

The ProLung report offers the test's conclusions regarding patients with lesions; 1) high risk for malignancy or 2) low risk for malignancy. With regulatory clearance, test results are to be used adjunctively with CT information and other risk factors to aid in the risk stratification of patients with indeterminate lung lesions that are suspicious for lung cancer.

3.3 Clinical Use

The ProLung unit is designed for ease of operation, service and reliable performance. The ProLung unit conforms with all applicable safety standards and has been designated as a *non significant risk device* in its previous IRB reviews. In preparation for investigational use, Fresh Medical Laboratories provides appropriate training. The ProLung provides screen prompts for essential subject information entry, and provides visual anatomic views to guide the operator through each measurement in the protocol sequence. The ProLung unit also provides visual and audible indications of measurement quality to the operator and the option of subject data measurement review by the operator.

3.4 ProLung Unit Physical Description

The ProLung unit measures 13.5" wide by 13.15" deep by 3.15" high and integrates proprietary hardware and a Microsoft Windows™-based computer system within the enclosure. Typical computer operator interface and peripheral equipment is attached to the device including mouse, display and keyboard. The proprietary diaphoretic electrodes and computer driven data acquisition probe are connected by cords to easily connect to matching color coded ports on the left side of the device body. The data acquisition probe uses a unique, single-use tip that makes contact with the patient's skin during the scan session. Marketed single-use kits will contain proprietary single-use tip and 6 (six) diaphoretic single-use adhesive reference electrodes. The patented probe design is critical to insure accurate and consistent measurements as described below. A printer may be attached to the system. The ProLung unit is a portable self-contained device.

3.5 Safety Information

The International Electrotechnical Commission (IEC) publishes the base standard 60601 that establishes limits for leakage current from a medical device at 150 microamps (0.000150 amps). The ProLung unit generates less than 10% of the allowable leakage current for medical devices. The instrument design includes industry approved isolation circuitry for use in clinical instrumentation.

The ProLung unit delivers a safe current of <25 micro amps to measure bioconductance between reference electrodes placed on the patient's back or hands and a computerized bioconductance probe placed sequentially at points on the skin surface. There is also safety information available from other currently marketed devices that introduce current into the body during usage. To cite two modalities, transcutaneous electrical nerve stimulation (TENS) and percutaneous electrical nerve stimulation (PENS)

are used for acute post-operative or chronic intractable pain[xxxviii] [xxxix]. TENS is characterized by biphasic current and most TENS units produce a current of 1 to 80 microampere (mA), 9 V (average), 2 to 1000 Hz, with a pulse width of 250 to 400 microseconds. PENS uses needles as electrodes that are placed in soft tissues or muscles at dermatomal levels corresponding to the local pathology. A 5-Hz frequency with a pulse width of 0.5 mS is usually used. Another FDA-approved device that delivers electrical stimulation is the ReliefBand[R] that is used to prevent or treat nausea and vomiting associated with motion sickness, pregnancy, or chemotherapy[xl]. Thus, the amount of electrical current that is associated with use of the ProLungis negligible and has not been nor is it expected to be associated with health risks or discomfort.

The reviewing IRBs for all previous studies conducted for the Sponsor have determined that the ProLung Testposed a non-significant risk to study subjects. In one ProLung study where 38 subjects were evaluated for safety, all completed the entire measurement session and none discontinued measurement due to discomfort or an adverse event (AE). There were two AEs as follows: one AE consisted of transient minor pain at a specific measurement point which was determined by the Principal Investigator to be unrelated to measurement because the skin was irritated prior to measurement, and the second AE was moderate pain and a tingling paresthetics sensation at a few measurement points in an elderly subject (94 years of age) who had a documented history of severe, symptomatic osteoarthritis as well as pain with touch on subject's skin. The symptoms rapidly resolved after measurement completion. The PI considered this AE to have a possible remote relationship to device use. The subjects overwhelmingly reported satisfaction with the measurement protocol and have indicated without exception that they would agree to be tested again. In the study with 22 normal subjects, none reported discomfort associated with use of the test. In the latest study at Johns Hopkins with 55 patients, there were also no reported adverse events.

The ProLung unit is manufactured under the Fresh Medical Laboratories ISO 13485 certified Quality Management System. The ProLung unit has also completed IEC 60601-1 and IEC 60601-1-2 safety testing.

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