

**CLINICAL TRIAL PROTOCOL**  
**(Phase IV - Efficacy Trial)**

**Medical Device: FDA K031876 ELECTRO FLO PERCUSSOR, MODEL 5000**

**Non-randomized, multisite site, single arm study for the efficacy of current FDA 510k indication for adults between the ages of 18 and 55 (non-smokers).**

**STUDY NUMBER: 2017-7**

**STUDY NAME: Med Systems Electro Flo 5000 Efficacy 2017**

**VERSION DATE: 15 December 2018**

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The logo for Mack Clinical Services, featuring the word "MACK" in a bold, black, sans-serif font. The letters are closely spaced, and the "M" and "A" are particularly prominent.

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**CLINICAL SERVICES™**

The Sponsor is: Med Systems, Inc.

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## **1.1 Study Synopsis:**

### **2.0 Sponsor's Intent and End Goals:**

This trial is in support of Med Systems® requesting a change in the HCPCS code for the Electro Flo® Percussor Model 5000 (hereby known as Electro Flo 5000) from E0840 Percussor, electric or pneumatic, home model to a new code E084x Airway Clearance System. E0840 is inadequate because:

- (1) E0840 is a broad category that includes percussors, vibratory massagers, and oscillatory sound wave devices.
- (2) The Electro Flo 5000 Force Multiplying Percussor and Self-Applicator System for Airway Clearance holds U.S. Patent No. 13/657,548. It consists of a programmable precision instrument that elicits sharp impacts combined with a strap for self-application to the front and back of the thorax as needed. The user controls power, speed, and force applied to obtain bronchial secretions and an improved O<sub>2</sub>/CO<sub>2</sub> gas exchange. Research has shown that greater percussive force applied results in a more effective treatment. The Electro Flo 5000 is the most powerful percussor available in airway clearance.
- (3) Insurers set the standard for reimbursement at the level of the lowest cost product within the code (vibratory massagers \$340-600) even though the clinical outcome of the Electro Flo Airway Clearance System (\$5,500) is comparable to that of High Frequency Chest Wall Compression (HFCWC) vests in a different code (E0483) which allows for reimbursement at a higher rate. A vibratory massager with a one-year warranty is the primary product being substituted for the Electro Flo 5000 Airway Clearance System with a three-year warranty.
- (4) The 7 lb. all-inclusive Electro Flo 5000 System provides compact, portable and effective treatment for loosening trapped mucus within the lungs to provide greater independence to the user. People who no longer find relief from vibratory massage or vests prefer it.
- (5) Use of the Electro Flo 5000 System helps persons avoid increased infections and hospitalizations.



### 3.1 LIST OF GENERAL ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Transaminase (liver enzyme)
AST	Aspartate Transaminase (liver enzyme)
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen (kidney function test)
C	Celsius
CAPA	Corrective and Preventive Action
CIOMS	Council for International Organizations of Medical Sciences
CK	Creatinine Kinase (muscle enzyme)
CRA	Clinical Research Associate
CRC	Clinical Research Coordinator
CRF	Case Report Form
CRO	Contract Research Organization
CTMS	Clinical Trial Management System
CV	Curriculum Vitae
DCF	Data Clarification Form
IDMC	Independent Data Monitoring Committee
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ePRO	Electronic Patient Reported Outcomes
eTMF	Electronic Trial Master File
EDC	Electronic Data Capture
EKG	Electrocardiogram
EMR	Electronic Medical Record
EHR	Electronic Health Record
F	Fahrenheit
FEV1	Forced Expiratory Volume in 1 Second
GCP	Good Clinical Practices
GI	Gastrointestinal
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices



hCG	Human Chorionic Gonadotrophin
HMO	Health Maintenance Organization
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IP	Investigational Product
IRB	Institutional Review Board
IEC	Independent Ethics Committee
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LAR	Legally Acceptable Representative
MAOI	Monoamine Oxidase Inhibitor
mcg	microgram
mmHg	Millimeters of mercury
NSAID	Non-Steroidal Anti-Inflammatory Drugs(s)
PI	Principal Investigator
PK	Pharmacokinetics
PRO	Patient Reported Outcomes
p.r.n.	as needed
QA	Quality Assurance
QC	Quality Control
QTc	ECG/EKG QT interval corrected for heart rate
RBCs	Red Blood Cells
RBM	Risk Based Monitoring
SAE	Serious Adverse Event
SDV	Source Document Verification
SMO	Site Management Organization
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
WBCs	White Blood Cells, or leukocytes



### **3.2 LIST OF SPECIFIC TRIAL ABBREVIATIONS**

**ATP:** Adult Treatment Panel.

**BID:** Twice daily.

**CEC:** Clinical Events Committee.

**CRF:** Case report forms.

**CT:** Computed tomography.

**DMC:** Data Monitoring Committee.

**DRF:** Discrepancy resolution form.

**GCP:** Good Clinical Practice.

**GMP:** Good Manufacturing Practices

**ICH:** International Conference on Harmonization.

**IP:** Investigational product.

**IRB/EC:** Institutional Review Board/Ethics Committee.

**ITT:** Intent-to-treat.

**MedDRA:** Medical Dictionary for Regulatory Activities.

**MRI:** Magnetic resonance imaging.

**OD:** Once daily.

**PSU:** Partial shipment unit.

**SAE:** Serious adverse event.

**ULN:** Upper limit of normal range.

**WHO:** World Health Organization.

**WOC:** Withdrawal of consent.



## **4. INTRODUCTION AND RATIONALE**

### **4.1 Role of the Electro Flo 5000**

#### **4.11 Introduction**

The Electro Flo 5000 Airway Clearance System is a therapy for the directing application of a percussive force to the chest wall to loosen mucus. The system is comprised of: (1) a Self-Administrator -- a self-applicator assembly including a first strap overlaying and substantially coextensive with a second strap, wherein the first and second straps are joined at their respective ends, and a pouch disposed between the first and second straps for directing the pulse generated by the percussor to the body; and (2) the Electro Flo 5000 Force Multiplying Percussor -- consisting of a hammer and anvil having a force-receiving surface and a force-delivering surface energized by an electric current and pulse generator. (See Attachment 1) Rapidly repeated impulses to the chest by the electronically cycled percussive hammer dislodges mucus adherent to airways within the lungs. Strategic placement of the system permits focused treatment of the affected lung regions. Patients apply the device directly to their frontal thorax or to their back by securing the device in the Self-Administrator and focusing the pulse where relief is desired. Users can apply Airway Clearance Therapy (ACT) directly on their back without the aid of another person.

The Electro Flo 5000's Force Multiplying Technology allows users to control the pulse frequency and pulse force of the impact through a combination of 30 independently adjustable settings. There are five power and six speed settings. The Electro Flo 5000's pulse force ranges from 15 to 35 pounds.

The broad range in pulse force and greater power of the Electro Flo 5000 is a function of its unique design. The device is comprised of over 200 parts constructed from specialized machined magnetic material and high-impact molded plastics.

The Electro Flo 5000 Airway Clearance System is an integrated approach to delivering care that is responsive to a patient's specific needs. It is a high-quality, high-value, cost-effective therapy.



#### **4.12 Clinical Application**

The Electro Flo 5000 Airway Clearance System is used to perform ACT. Patients with pulmonary diseases characterized by excess mucus generation, chronic infection, and inflammation of the airways with progressive destruction and loss of pulmonary function such as cystic fibrosis, COPD, or bronchiectasis require daily ACT.<sup>1</sup> Excess mucus caused by impaired mucociliary clearance can serve as a culture medium for pathogens, thereby increasing the rates of infection and inflammation as well as the rate of deterioration of lung function. By placing the Electro Flo 5000 on the thorax front or back and controlling the extent of the percussive force, a patient can break up and move the accumulated mucus from the small airways to the large, central airways of the lungs to be coughed out. (See Attachment 2)

Traditionally, ACT consists of manual percussion combined with postural drainage. The manual removal of mucous through airway clearance is the primary therapy for cystic fibrosis and results in the removal of excess mucous from lungs. However, manual percussion is time and labor intensive, and depends on a therapist or trained individual to perform the therapy on the patient. These disadvantages are most evident when patients undertake the treatment at home since poor compliance with the prescribed therapeutic regime can be an issue, especially among active individuals who work, travel, go to school or otherwise spend time away from home.

The Electro Flo 5000 Airway Clearance System is preferable to manual percussion (and other therapies such as a vibratory massager) on multiple counts. It relieves a patient of the physical demands of hand percussion while at the same time generating stronger impacts and does not require the application by another person. It gives individuals maximum control over where and how ACT is applied. And because it is lightweight and portable, ACT can be performed when and where it is needed.

To use the Electro Flo 5000, a patient either cups the percussive device in their hand or straps it into the Self-Administrator with the percussive head placed against the body. The patient adjusts the settings for the pulse force and speed on a control box. Pressing harder on the area where it is applied increases the impact force. Use of the Electro Flo 5000 alone is sufficient for the



frontal thorax while addition of the Self-Administrator makes it possible for a patient to reach individual back lobes.

#### **4.13 Potential Participant Demographic**

The Electro Flo 5000 is cleared by the U.S. Food and Drug Administration for use in the home, or institutional and hospital settings when the physician's choice of therapy is external manipulation of the thorax due to evidence of retained secretions.

It is indicated for use by individuals with: cystic fibrosis; bronchiectasis; chronic bronchitis; chronic obstructive pulmonary disease (COPD); chronic emphysema; occupational lung disease; pneumonia; pulmonary edema; asthma; neuromuscular diseases such as Guillain-Barre syndrome; progressive muscle weakness such as myasthenia gravis; lung abscess; tetanus; cerebral palsy; muscular dystrophy; AIS; and other lung obstructive conditions.

A major user population consists of those with cystic fibrosis (CF). CF is the most common life-shortening disease among Caucasians. In the US, there are close to 30,000 affected individuals.<sup>2</sup> The disease affects all exocrine glands. When it was described as a distinct clinical entity 60 years ago, it was usually fatal during the first year of life. Better understanding of the disease pathophysiology, as well as advances in medical therapies, has led to a continuous improvement in the survival and quality of life of affected individuals<sup>3</sup>, with the current median age of survival being approximately 39 years.<sup>4</sup>

#### **4.14 Classification of Device**

The Electro Flo 5000 Airway Clearance System is indicated for use by patients with a diagnosis characterized by excessive mucus production and difficulty clearing secretions (e.g. cystic fibrosis, bronchitis, bronchiectasis, COPD, and pulmonary edema, among others). This system mimics and enhances the relief gained from manual chest physiotherapy.

Airway clearance devices are designed to deliver percussions to the chest wall or cause oscillatory air pressure changes to the airways that liberate obstructive airway secretions. The following are HCPCS codes associated with these devices:



- A. Flutter Device - S8185
- B. Oscillatory positive expiratory pressure (OEP) device - E0484
- C. Intrapulmonary percussive ventilation system - E0484
- D. High-frequency chest wall oscillation air-pulse generator system - E0483
- E. Percussor, electric or pneumatic, home model - E0480

1. Mechanism of Operation -- The mechanism driving the different devices listed in E0840 consist of: (a) an off-center motor-driven weight that shakes the applicator head (GS Vibracare and Flimm Fighter); (b) an oscillating pneumatic valve that cycles the percussive device (Fluid Flo 2500); and an electronically cycled solenoid that supports independent adjustment of pulse force and frequency (Electro Flo 5000). Only the latter two are true percussors.
2. Type of Impact - In contrast to the other devices, the Electro Flo 5000 is the only one capable of producing a 35lb. impact similar to a hammer blow. This difference is visible in the waveforms created by each instrument. While the other devices produce evenly spaced waves, the Electro Flo 5000 creates sharp amplitudes. (See Attachment 4) This too, distinguishes the true percussor (Electro Flo 5000) as opposed to the GS Vibracare and Flimm Fighter. The other technologies attempt to deliver a percussive-like impact through a vibratory massager. True percussors are have more complicated mechanics than vibratory massagers, contain more working parts, and are able to impart much greater pulse force.
3. Pulse Force -the Electro Flo 5000 is significantly distinct therapeutically from other products because it provides a percussive impact as opposed to the GS Vibracare or Flimm Fighter that are vibratory percussive massagers. Comparative pulse force tests of the Electro Flo 5000 show that it generates significantly more pulse force than the other products. The GS Vibracare has 10 settings that can deliver a pulse force ranging from 2.9 to 10.75 lbs. The Flimm Fighter has 11 settings able to deliver a pulse force ranging from 1.5 to 13.75 lbs. The Fluid Flo 2500 has 4 settings and is able to reach a pulse force ranging from 17.2 to 19.0 lbs. The Electro Flo 5000, on the other hand, has 30 settings with the ability of reaching a pulse force ranging from 15.0 to 33.7 lbs. (See Attachment 5) Greater pulse force has been found to have more therapeutic value among cystic fibrosis patients. Research published in the journal Respiratory Care draws a clear relationship between higher pressure and greater relief among cystic fibrosis patients.' The Electro Flo 5000 with Force Multiplying Technology has 30-targeted settings. Power and frequency can be precisely directed to individual lobes of the lungs. The independent adjustment of power and speed in contrast to other devices,



gives patients greater ability to select the specific combination desired and direct the percussive power where needed. Respiratory therapists emphasize that lung clearance includes getting air behind the mucus in order to move it up and out of the airways while achieving greater sputum expectoration.<sup>6</sup> With the Electro Flo 5000 with Force Multiplying Technology, patients control the movement and directionality of the obstruction whether from the front or the back. This capability is significantly different from the vest, which does not permit directed therapy or the GS Vibracare or Flimm Fighter since they lack percussive power. With the Electro Flo 5000, patients can achieve more effective treatment, such as adults who require vigorous pounding to release the congestion, or those with long lobes not reached by vests.

4. Unit Cost-The Electro Flo 5000 is a true percussor distinguished by its ability to deliver more powerful impacts than vibratory massagers. To impart its distinctive sharp and strong pulse force requires more complicated mechanics than vibratory massagers; it is made from specialized machined magnetic materials and high-impact molded plastics and is comprised of over 200 parts. As a result, it costs approximately ten times more than the vibratory massagers, yet half the cost of vests.

This is the crux of the problem. Depending on the state, insurers will only reimburse between \$340 and \$600 the cost of vibratory massagers. Although the Electro Flo 5000 Airway Clearance System requires a prescription and in many cases is the only product that works for patients, insurers have determined what they consider to be a 'standard percussor' and the Electro Flo 5000 is excluded from their definition. Consequently, they will only pay for a vibratory massager.



#### **4.15 Adverse Medical Device Reactions / Medical Device Interactions**

*None*

#### **4.16 Administration of Ultrasound**

*None*

#### **4.17 Clinical Recommendations**

Please see FDA 510K Indications

#### **4.18 Medical Device Interactions**

Not designed to be used in combination with any other medical devices unless specified by ordering physician.

#### **4.19 Precautions and Warnings**

Please see device manual and instructions.

#### **4.2 Rationale for Evaluating the Beneficial Effect of Electro Flo 5000 with Adult Participants.**

##### **4.21 Key Facts**



#### **4.22 Device Description**

Trade/Device Name: Electro Flo Percussor, Model 5000

Regulation Number: 21 CFR 868.5665

Regulation Name: Percussor, Powered-Electric

Class: Class II

Product Code: BYI

#### **4.23 Performance Data**

Please see User Manual

#### **4.24 Substantial Equivalence Summary**

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

#### **4.25 Proposed Device Indications**

No Change

#### **4.26 Predicate Device**

510(k) Number - K802399



#### **4.27 Submitting Entity**

MED SYSTEMS

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San Diego, CA 92117

Phone 800.345.9061 Fax 858.483.9827

www.medsystems.com

#### **4.28 Classification Regulation**

Trade/Device Name: Electro Flo Percussor, Model 5000

Regulation Number: 21 CFR 868.5665

Regulation Name: Percussor, Powered-Electric

Class: Class II

Product Code: BYI

#### **4.29 Indication(s)**

The intended use of the Med Systems Electro Flo Percussor Model 5000 is the same as the predicate device, which is to provide airway clearance therapy when external manipulation of the thorax is the physician's choice of treatment. Indications for this form of therapy are described by the American Association for Respiratory Care (AARC) in the Clinical Practices Guidelines for Postural Drainage Therapy ('I (1991). According to AARC guidelines, specific indications for external manipulation of the thorax include evidence or a suggestion of retained secretions, evidence that the patient is having difficulty with the secretion clearance, or presence of atelectasis caused by mucus plugging. In addition, the Med Systems Electro Flo Percussor Model 5000 is also indicated for external manipulation of the thorax to promote airway clearance or improve bronchial drainage for purposes of collecting mucus for diagnostic evaluation.

(1). Bronchial Hygiene Guidelines Committee, American Association for Respiratory Care. AARC clinical practice guideline: postural drainage therapy. Respiratory Care 1991; 36: 1418 - 1426.



Prescription Use X  
(Per CFR 801 Subpart D)

No parts are sterilized from the manufacturer. The clinician is responsible for all cleaning and cleanliness of the device in accordance with standard of care procedures.

#### **4.3 Rationale for this Trial Design**

Since this study is designed to illustrate the efficacy of the device for the current 510K indications in a single arm, large sample multisite study. A placebo control is not required since each subject will serve as a before and after treatment with measurable indicators.

### **5. STUDY OBJECTIVES**

#### **5.1 Primary Objective**

To specifically illustrate and measure both clinical and empirical efficacy described by (AARC) in the Clinical Practices Guidelines for Postural Drainage Therapy (1991) for external manipulation of the thorax for postural drainage therapy and the secretion clearance, or presence of atelectasis caused by mucus plugging.

Outcome measured by:

Percentage change of oxygen levels in the blood (pulse oximetry). SpO2 will be monitored using the standard pulse oximeter system (K131111). Change from baseline before treatment and measure again up to 3.5 hours after treatment.



## **5.2 Secondary Objective**

To observe the quality of lung function that participants experience during the use of the device during the trial period.

Outcome measured by:

Percentage change of lung function. Evaluate expiratory forced vital capacity (FVC) and forced expiratory volume (FEV1) will be monitored with standard spirometer. Change from baseline before treatment and measure again up to 3.5 hours after treatment.

## **5.3 Other Objectives**

N/A

# **6. STUDY DESIGN**

## **6.1 Description of the Protocol**

The present study is designed as a multi-center, non-randomized, single-blind, one arm group trial with 70 participants per arm.

## **6.2 Duration of Study Participation**

The estimated study duration that served as the assumption for sample size calculations is eleven (24) month. Each participant shall be active in the trial for a period of 21 days following enrollment. All participants will be followed to a common study end date, which is estimated to occur when the last randomized patient has been followed for two (2) months, based on a one (2) week recruitment period.

## **6.3 Interim Analysis**

Interim analysis during this study shall be conducted at Day 7, 14 and 21 for the 70 participants to ensure participant safety before the other participants enter into the trial.



## **6.4 Study Committees**

The Mack Biotech, Corp. group will be in charge of the logistical coordination of the different study committees. Distinct responsibilities of Mack Biotech, Corp. and the study Sponsor are provided in Appendix 1.

### **Executive Committee**

The Executive Committee of the study is composed of Investigator/Academic Members from participating countries and Sponsor Representatives. This Committee, led by its Chairman, Leigh J. Mack, MD (Sponsor Lead Researcher), who will provide scientific and strategic direction for the trial and will have overall responsibility for its execution. Detailed responsibilities and membership for this committee are provided in Appendix 2.

### **Operations Committee**

The Operations Committee is responsible for ensuring that study execution and management are of the highest quality. This Committee will be composed of the Chairman and co-Chairmen of the Executive Committee, as well as the National Principal Investigator and nonvoting Sponsor Representatives. It will determine its own guidelines and approve the criteria and guidelines of the other Committees prior to commencement of the study. The Operations Committee will convene regularly (at least every month) to discuss and report on the progress of the study. Detailed responsibilities and membership for this Committee are provided in Appendix 3.

### **Clinical Events Committee (CEC)**

The CEC is composed of multidisciplinary academic members. This Committee, coordinated by Mack Biotech, Corp., will be responsible for validating and classifying, in a blinded fashion, all the primary efficacy outcome events reported by the Investigators. Detailed responsibilities and membership for this Committee are provided in Appendix 4.

### **Data Monitoring Committee**

The Data Monitoring Committee (DMC) is composed of Academic Members who are not otherwise participating in the trial. This Committee, led by its Chairman, Mack Biotech, Corp. will be responsible for the monitoring of patient safety, and it will be supported by an external DMC-associated statistician. Detailed responsibilities and membership for this Committee are provided in Appendix 5.



The DMC can request any analysis during the course of the study, on either a blinded or unblinded basis.

The independent DMC-associated statistician will perform the planned analyses as well as the other analyses requested by the DMC, independently from the Sponsor. This independent statistician will be provided with the randomization code list, as well as with regular database transfers. He/she will prepare pro-forma tables, listings, and a report for submission to the DMC. Safety data will include serious adverse events (SAEs), outcome events, local laboratory values, plus other adverse events (AEs) as requested by the DMC. Demography, treatment and trial status data will be presented as requested by the DMC. The report will be based on current data, whether clean or not, and whether adjudicated or not. Although efficacy data will be provided, DMC review of these data does not constitute a formal interim analysis of efficacy, and any analyses of these data will not, in and of themselves, be used for stopping the trial.

## **7. SELECTION OF PROCESS OF PARTICIPANTS**

### **7.1 Number of Participants Planned**

Based upon the anticipated event rates, premature treatment discontinuation and expected relative efficacy, approximately 70 participants will be enrolled in the study, with approximately 70 participants in each arm.

### **7.2 Inclusion Criteria**

- Previously diagnosed with cystic fibrosis (mild, moderate or severe)
- Prescribed (licensed medical provider) airway clearance device/system for at home, self-treatment for airway clearance
- Physically able to perform self-treatment or treatment by an at home medical provider



### **7.3 Exclusion Criteria**

- History of tobacco use
- History of excessive alcohol consumption, more than 2 drinks per day, 10 per week
- Any other medical condition that would preclude use of an airway clearance device
- Previously diagnosed with major cardiological disease

#### **7.3.1 Related to General Patient Characteristics**

1. Presence of any severe medical or psychological condition that, in the opinion of the Investigator, would compromise the participant's safe participation.
2. Immunocompromised by other types of viral infections or has a history of any other hepatitis form e.g. types A, C, D, E.
3. Underlying diseases or other dermatologic conditions that require the use of interfering topical or systemic therapy or that might interfere with study assessments such as, but not limited to, atopic dermatitis or herpes zoster (shingles). This includes clinically significant abnormal findings, uncontrolled or serious disease, or any medical or surgical condition, that may either interfere with the interpretation of the clinical trial results, and/or put the subject at significant risk (according to Investigator's judgment) if he/she participates in the clinical trial.
4. The subject has received, applied or taken some specified treatments within the specified timeframe prior to the Baseline visit
5. The subject is unwilling to refrain from use of prohibited medication during the Clinical Trial.
6. N/A
7. Presence of any condition (medical, psychological, social, or geographical), actual or anticipated, that the Investigator feels would restrict or limit the participant's successful participation for the duration of the study.



8. Receipt of any investigational treatment (medical device or drug) within 30 days prior to baseline visit.

9. Previous participation in a Electro Flo 5000 medical device study.

10. Known allergy to any components of the device itself (e.g. plastics/polymers).

### **7.3.2 Related to Other Conditions**

None

## **8. TREATMENTS**

### **8.1 Medical Device Description**

The Electro Flo 5000 is intended to assist in airway clearance therapy when the physician's choice of therapy is external manipulation of the thorax. Additionally, the Electro Flo 5000 is indicated for external manipulation of the thorax to promote airway clearance and improve bronchial drainage.

### **8.2 Description of Blinding Methods**

Final data analysis shall be completed by a third party, data analysis and reporting agency.

### **8.3 Method of Assigning Participants to Treatment Group**

N/A - All included shall be assigned to the single arm.

### **8.4 Packaging and Labeling**

Please see User Manual and instructions along with physician prescription.

### **8.5 Storage Conditions**

Please see User Manual



## **8.6 Access to the Randomization Code During the Study**

N/A for this trial

The Investigator will be supplied with participant information if medically needed or required for safety from the Sponsor.

Additional unblinding materials will be available and are to be kept in a safe place at CRU level (or subcontractor, if any) throughout the clinical trial. The Sponsor will retrieve all envelopes, whether opened or sealed, on study completion.

In case of a Serious Adverse Event, the code should be broken only in exceptional circumstances when knowledge of the Investigational Product is essential for treating the patient.

In case the physician at the investigational site believes unblinding is needed, he/she must first contact the Medical Advisor located at Mack Biotech for further direction. All calls will be documented as appropriate to include date and time of the call, name of the Optional Study Group Medical Advisor, name, qualification, and address of the physician contacting Optional Study Group, patient ID, documentation of the request, and decision for unblinding or not.

If possible, a contact should be initiated with the Monitoring Team before unblinding. In case the decision to unblind is made, the Investigator must document it with the date, time of day, and reason for unblinding, and report this information in the appropriate page of the CRF and source document.

Note that when documenting the reason for unblinding, the Investigator must not provide any detail regarding the nature of the Investigational Product. The Investigator should not divulge medication detail to any Med Systems, Inc., or Mack Biotech, Corp. staff member, Sponsor's representative, or to any Study Committee members until database closure. Furthermore, when completing forms (eg, AE, SAE), the study treatment should not be disclosed on the forms. The unblinding envelopes will be sealed again and stored at the site level until the end of the study (envelopes opened by the CRU or a subcontractor must also be sealed again).



## **8.7 Responsibilities**

The Investigator or other personnel allowed to store and dispense Investigational Product (IP) will be responsible for ensuring that the IP used in the study is securely maintained as specified by the Sponsor and in accordance with the applicable regulatory requirements.

All IP shall be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record of IP issued and returned is maintained.

Any quality issue noticed with the receipt or use of an IP (deficient IP in condition, appearance, pertaining documentation, labeling, expiry date, etc) should be promptly reported to the Sponsor, who will initiate a complaint procedure.

Under no circumstances will the Investigator supply IP to a third party, allow IP to be used other than as directed by this Clinical Trial Protocol, or dispose of IP in any other manner.

## **8.8 Retrieval and/or Destruction of Investigational Product**

All partially used or unused treatments will be retrieved by the Sponsor. A detailed treatment log of the returned IP will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the Monitoring Team.

The Investigator will not destroy unused IP unless the Sponsor provides written authorization to the contrary.

A potential defect in the quality of IP may be subject to initiation by the Sponsor of a recall procedure. In this case, the Investigator will be responsible for promptly address any request made by the Sponsor, in order to recall IP and eliminate potential hazards.

## **8.9 Concomitant Treatment**

None

### **8.9.1 Prohibited Concomitant Treatment**

None



### **8.9.2 Permitted Concomitant Treatment**

Any medical devices other than those listed above are allowed, and should be administered, as necessary for the treatment of the patient, when possible with a stable dose, at the discretion of the Investigator. All treatment with these medical devices should be recorded on the appropriate CRF.

### **8.10 Treatment Compliance**

Compliance is assessed by counting the number of returned bottles if any at each visit. The Investigator (or delegate) must complete the appropriate pages of the treatment log form and of the CRF. A discontinuation is defined as a period with a least three consecutive days without study medical device intake.

The study shall be open enrollment but patients must have access to the clinical location for clinical survey reporting. The survey must be completed two (2) times per week during the 21 day long trial. Potential participants should reside in the United States.

The monitor supervising the study will verify the data by comparing the recorded data with the investigational product retrieved.

### **8.11 Participant Reimbursement**

Participants shall be reimbursed at a rate of seven dollars (\$7.00) per day for each day that data for the two objectives is sent to the Principal Investigator. The reimbursement is provided for the participant's time for recording the data on a personal smart device, the cost of data transfer and overall phone costs for sending the information to the Principal Investigator. The total reimbursement amount that may be provided to the participant is no more than \$210.00. The reimbursement shall be provided to the participant, by the Sponsor, after the participant completes the trial period by company check paid to the participant.

## **9. ASSESSMENT OF INVESTIGATIONAL PRODUCT**

### **9.1 Efficacy**

The goal of this trial is to illustrate before and post treatment changes measured by spirometer.



### **9.1.1 Efficacy Criteria**

Primary: Physical exam by medical practitioner for initial diagnosis and changes in spirometer reading from before treatment compared to reading three (3) hours after treatment. In addition, changes in iHealth Air pulse oximeter (FDA 510k K131111) reading from before treatment compared to reading three (3) hours after treatment.

#### **9.1.1.1 Primary Criterion**

Composite success rate. Safety - no issues or reported adverse conditions.

#### **9.1.1.2 Secondary Criterion**

Percent change of spirometer reading from before treatment compared to three (3) hours after treatment by the participant. Subjective participant opinion of the efficacy provided by semi-weekly surveys.

### **9.1.2 Clinical Assessment Methods**

Primary: Measurements of before and after with pulse oximetry device and spirometer.

Secondary: Participant surveys completed.

#### **9.1.2.1 Definitions of Components of the Primary Efficacy Endpoint**

N/A



## **10. PATIENT SAFETY**

### **10.1 Adverse Events Monitoring**

#### **Definitions:**

An adverse event is any untoward medical occurrence in a clinical investigation participant administered a medical device and which does not necessarily have to have a causal relationship with this treatment.

A Serious Adverse Event is any untoward medical occurrence at any dose that:

- Results in death or;
- Is life-threatening or;  
Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization or;
- Results in persistent or significant disability/incapacity or;
- Is a congenital anomaly/birth defect;
- Is a medically important event:  
Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.



## **Adverse Events**

All Adverse Events regardless of seriousness or relationship to Investigational Product, including those from the first visit planned in the Clinical Trial Protocol/signature of the informed consent form, are to be recorded on the corresponding page(s) included in the Case Report Form. Whenever possible, symptoms should be grouped as a single syndrome or diagnosis. The Investigator should specify the date of onset, intensity, action taken with respect to Investigational Product, corrective treatment/therapy given, outcome and his/her opinion as to whether there is a reasonable possibility that the Adverse Event was caused by the Investigational Product.

## **Serious Adverse Events**

In the case of a Serious Adverse Event the Investigator must immediately:

- SEND (within 1 working day, by email) the signed and dated corresponding page(s) in the Case Report Form to the representative of the Monitoring Team whose name, address and email number appear on the Clinical Trial Protocol, or to a designated Safety email number provided by the Monitoring Team, as well as to the Central Database number;
- ATTACH a photocopy of all examinations carried out and the dates on which these examinations were performed. Care should be taken to ensure that the participant's identity is protected and the participant's identifiers in the Clinical Trial are properly documented on all copies of source documents provided to the Sponsor. For laboratory results, include the laboratory normal ranges;
- Follow-up of any Serious Adverse Event that is fatal or life threatening should be provided within one additional calendar week. The treatment code will be unblinded for reporting of Serious Adverse Events that are unexpected and reasonably associated with the use of the Investigational Product.

Serious Adverse Events Follow-up



- The Investigator should take all appropriate measures to ensure the safety of the participants, including referral to a specialist if indicated. Notably he/she should follow up the outcome of any adverse events (clinical signs, laboratory values or other, etc) until the return to normal or stabilization of the participant's condition;
- In the case of any serious adverse event, the patient must be followed up until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized. This implies that follow-up may continue after the patient has left the Clinical Trial and that additional investigations may be requested by the Monitoring Team;
- In case of any serious adverse event brought to the attention of the Investigator at any time after cessation of Investigational Product and considered by him/her to be caused by the Investigational Product with a reasonable possibility, this should be reported to the Monitoring Team.

## **10.2 Pregnancy**

No known adverse interactions with pregnant or nursing mothers.

## **10.3 Waiver**

Expected efficacy endpoints specified in this trial (primary and secondary efficacy criteria) will not be considered as AEs and will not be subject to expedited regulatory reporting. They will be reported on specific outcome event forms, which should be sent within one (1) working day, by Email, to the Central Database number.



## **11. HANDLING OF PATIENT WITHDRAWAL**

### **11.1 List of Withdrawal Criteria**

Occurrence of an outcome event according to the judgment of the Investigator must not be considered as a reason for study medical device discontinuation.

Depending on the Investigator's judgment, permanent study medical device discontinuation is only clearly justified for an adverse event, when qualifying condition is not present, or when a patient demands to withdraw from study medical device treatment, and in such cases the appropriate follow-up until the study end date should still be continued.

Although participants may withdraw from the study medical device at any time and for any reason, (or may be withdrawn at the Investigator's decision), patient withdrawal should be avoided as much as possible. If this occurs, every attempt should be made to restart study medical device if medically appropriate, whatever the duration of discontinuation. The reason for study medical device discontinuation will be recorded on the CRF. In any case, appropriate follow-up for efficacy and safety endpoints should be continued.

### **11.2 Follow-up Procedures After Withdrawal**

Participants who prematurely discontinue study medical device are not to be replaced.

All randomized participants must be followed up according to the study flowchart until study end date or death, regardless of whether they discontinued study medical device prematurely or not. Any event occurring after early study medical device discontinuation will be recorded up through the study end date.

In case of study medical device discontinuation (temporary or permanent) due to an adverse event, such participants will be closely monitored until the resolution or stabilization of this adverse event. This may mean that follow-up will continue after the participants have completed the study follow-up. Although data on that adverse event will continue to be captured, even beyond the last visit, for new efficacy or safety events, only those that occur up through the last visit should be recorded.



In case of written withdrawal of consent (WOC) for follow-up visits, and unless otherwise stated by the patient in the informed consent form, Investigators will be encouraged to get information from the general practitioner, any other physician, or other medical-care provider, in order to follow the medical status of the participants (especially when they withdraw their consent after having experienced an AE/SAE or an efficacy endpoint). Investigators will also be expected to try as much as possible to re-contact those participants at the end of the trial, in order to obtain at least their follow-up of the efficacy assessment.

For participants considered lost to follow-up, the CRF must be completed up to the last visit performed.

### **11.3 Consequence**

If the medical device is stopped prematurely, every attempt should be made to restart it if medically appropriate, whatever the duration of discontinuation.

If the patient withdraws his/her consent for study participation, although in such circumstances he/she may not be obliged to comply with all the protocol visits and phone calls, the Investigators, the study nurses and any other study coordinators are requested to try to obtain as much as possible, the vital status of the patient at study end date. This will be clearly stated in the informed consent form.

Any direct communication with the general practitioner, any other physician or other medical-care provider can be helpful for following the medical status of the patient. This is particularly important if the patient withdraws his consent after experiencing an AE/SAE or an efficacy endpoint since for safety and Regulatory purposes, it is necessary to obtain some information regarding worsening or resolution of the event (especially if this event is considered as to be related to the Investigational Product).

In addition to the need for safety assessment, it is also important to avoid any lost to follow-up participants for the efficacy assessment and meaningful analysis of the study.



## **12. STUDY PROCEDURES**

### **12.1 Visit Schedule**

After initial contact and pre-qualification through enrollment in person. The participant shall be provided with an appointment for enrollment. Patient shall provide full medical history with any known pulmonary, cardiovascular or neurological diagnosis. This decision shall be that of the PI and the clinical health care provider at the location of the trial.

#### **12.1.1 Pre-Screening Procedures**

Study participants will be recruited from email list recruitment, clinics, and diagnostic centers, under the responsibility of a participating Investigator. Prior to initiation of the recruitment phase, participating Investigators will identify a pool of potential study subjects. Each of these centers will identify potentially eligible participants in advance,

#### **12.1.2 Baseline Visit**

The patient will receive complete information about the study in writing and orally if they choose. Written informed consent must be obtained from the patient prior to any study-specific procedures and prior to randomization. Compliance with inclusion criteria (listed in Section 7.2) and exclusion criteria (listed in Section 7.3) will be checked on the basis of information collected, and recorded in the CRF.

Key baseline patient characteristics obtained at the randomization visit will be recorded in the CRF, including demographics, height, weight, relevant past medical and surgical history, including neurological and psychiatric history, and abnormalities noted on physical exam, including any past dermatology exams.

Medical history, physical examination, laboratory, or instrumental results confirming inclusion and absence of exclusion criteria will be maintained in the participant's file.



## **12.2 Inclusion Procedures**

Once all inclusion/exclusion criteria are fulfilled, the patient becomes eligible for randomization and inclusion into the treatment period. Treatment allocation will be performed as stated above (Section 8.3). Study kit will be delivered as stated in Section 8.4.

Participants will be counseled to follow a healthy diet, to increase their water consumption and to stop smoking, if they are smokers.

## **12.3 Description by Type of Visit**

- Baseline enrollment form completed and submitted online (secure site), informed consent signed and submitted.
- Follow up call, email and follow up summary completed by the Investigator at the end of the one month treatment period with written results.
- Three (3) month participant courtesy email to confirm safety and answer any questions.

**There is no strict timing for the phone calls. In any case, it is better to call the patient after a delay, than to not call them at all (even in this case, the phone call record page of the CRF should be completed).**

The patient visit schedules will be given by the Investigator as soon as the participant is randomized, so as the Investigator can plan in advance all the necessary appointments with the participant.

## **12.4 Definition of Source Data**

All the data collected in the CRF come from source documents that are part of the patient dossier. Copies of some of those source documents will be collected after anonymization, in order to support documentation of outcome events eligible for validation by the Clinical Events Committee, ie:

.



## **13. STATISTICAL CONSIDERATIONS**

### **13.1 Statistical and Analytical Plans**

The material of this section is the basis for the Statistical Analysis Plan of this study. This plan may be revised during the study to accommodate Clinical Trial Protocol Amendments and to make changes to adapt to unexpected issues in study execution and data that affect planned analyses. These revisions will be based on blinded review of the study and data, and a final plan will be issued prior to data lock.

### **13.2 Determination of Sample Size**

Based on the targeted population for the study of 30,000 patients, 70 participants is considered a reasonable assumption for the yearly representational event rate in the group. Assuming recruitment over a 16 month period, and a total study duration of 24 months, 70 participants per group has been historically significant for prior trials designed to illustrate clear efficacy of a device as it relates to the United States CMS for this category of device.

### **13.3 Study Patient Description**

No specifics other than the trial inclusion parameters.

#### **13.3.1 Disposition of Participants**

The number of randomized participants will be summarized by county and center using counts and percentages. The number of participants either completing or permanently discontinuing the study medical device period will be summarized using counts and percentages.

#### **13.3.2 Clinical Trial Protocol Deviations**

All the following deviations will be summarized on the all randomized patient population:



- Inclusion or exclusion criteria not satisfied.
- Deviations related to the study medical device administration
- Not permitted concomitant medications.

## **13.4 Data Analysis Considerations**

### **13.4.1 Dataset Analyzed**

#### **13.4.1.1 Treatment Group Considered for Statistical Analysis**

For all efficacy and safety analyses, participants will be included in the treatment group to which they were originally allocated by the PI.

#### **13.4.1.2 Populations to be Analyzed**

The intent-to-treat (ITT) population will be used for all efficacy and safety analyses. This will consist of all randomized participants irrespective of whether the patient actually received study medical device or the participant's compliance with the study protocol, in the treatment group assigned by the software system. A patient will be considered randomized as soon as they are assigned to the group, after proper consent.

#### **13.4.1.3 General Statistical Approach**

All statistical tests will be two-sided.

All summary tables for quantitative parameters will display mean, standard deviation, median, range (minimum and maximum), as well as number of missing data (if relevant). All summary tables for qualitative parameters will display counts, percentages and number of missing data if relevant.



Baseline data are defined as the last measurement performed before the first study medical device intake.

### **13.4.2 General Convention**

#### **13.4.2.1 General Rules for Handling of Missing, Unused or Inconsistent Data**

In general, missing values will remain as missing, i.e., no attempt will be made to impute missing values and only observed values will be used in data analyses and presentations. Specific rules for handling missing efficacy data are described in Section 13.7.1.2.1.

#### **13.4.2.2 Other Specific Conventions**

### **13.5 Demographic and Baseline Characteristics**

No specifics other than the trial inclusion parameters.

#### **13.5.1 Patient Demographic Characteristics, Medical History and Diagnoses**

Baseline characteristics will be described using the ITT population. Demographics, medical history and other baseline variables will be summarized as appropriate to the type of data.

#### **13.5.2 Previous Medications**

In order to further characterize the study population, the incidence of the use of selected medications should be disclosed by the participant to include: Any current or passed drugs directly prescribed or used to treat cystic fibrosis (CF).

### **13.6 Investigational Product and Concomitant Therapy**

Not applicable to this Clinical Trial.



### **13.6.1 Investigational Product**

#### **13.6.1.1 Extent of Exposure**

The duration of study medical device treatment (accounting for permanent discontinuation) will be summarized. The number of participants on treatment over time will be summarized. The total patient years on study medical device will also be calculated

#### **13.6.1.2 Measurement of Treatment Compliance**

Treatment compliance for each patient will be calculated as the number of days study medical device was actually used (ie, number of days on treatment minus days of temporary discontinuation) divided by the number of days of follow-up, allowing for early permanent discontinuation of study medical device when applicable. Study medical device discontinuation is defined as a minimum of 3 consecutive days without study medical device intake. The percentage of participants at least 80% compliant will also be reported.

### **13.6.2 Concomitant Medication/Therapy**

Not recommended for this Clinical Trial - however, if deemed medical necessary then the appropriate treatment should be administered as ordered by the physician.

## **13.7 Efficacy/Activity Analysis**

The main efficacy measurement shall be a reduction the appearance of cystic fibrosis (CF).

### **13.7.1 Primary Efficacy Variable(s)**

A reduction in the appearance of cystic fibrosis (CF).

#### **13.7.1.1 Description of the Primary Variable(s)**

The primary efficacy endpoint is the composite cluster of the first occurrence, over the duration of study (randomization to study end date inclusive), of the following adjudicated events:



- Any skin conditions caused by the device to include irritations,
- Any allergic reactions,
- Any new medical conditions during the study.

### **13.7.1.2 Primary Analysis**

#### **13.7.1.2.1 Handling of Dropouts or Missing Data**

All randomized participants will be included in the primary ITT efficacy analysis. Participants not reaching the primary efficacy endpoint by the study end date, or before their last assessment for participants lost to follow-up, will be censored at the date of their last assessment visit.

#### **13.7.1.2.2 Data Transformation Before Analysis, If Any**

No data transformation will be applied to raw data.

#### **13.7.1.2.3 Main Statistical Model and Adjustment for Covariates**

For the primary analysis, all adjudicated events occurring from randomization to the study end date (inclusive) will be counted, including events occurring after early permanent discontinuation of study medical device. The proportion of participants remaining event-free over time will be displayed in the form of survival curves using the Kaplan-Meier method and analyzed (primary analysis) using a two-sided log-rank test. Statistical significance will be claimed if the computed p-value is equal to or less than 0.05.

The number and percentage (crude rate) of participants experiencing a primary endpoint will be summarized.



#### **13.7.1.2.4 Multiple Comparisons/Multiplicity**

If the primary efficacy reaches statistical significance, then the two secondary endpoints will be formally tested at the 5% level in a hierarchical (step-down) procedure.

#### **13.7.1.2.5 Other Analyses for Primary Variable(s)**

In order to further investigate the primary endpoint the following analysis will be done:

**Subgroup Analysis:** The incidence of the primary efficacy endpoint will be summarized by a number of covariates including age, gender, and race to examine their potential effects. Each of these factors will be analyzed statistically using a Cox proportional hazards model incorporating terms for treatment, the covariate and the treatment-by covariate interaction. The number of participants with outcomes, estimated hazard ratios, and associated 95% confidence intervals will be calculated within each of the subgroups generated by these analyses.

### **13.7.2 Secondary/Other Efficacy Variables**

#### **13.7.2.1 Description of Secondary/Other Variables**

Secondary endpoint: The composite cluster of the first occurrence, over the duration of study (randomization to study end date inclusive), of the following cluster of events:

#### **13.7.2.2 Statistical Analysis of Secondary/Other Variables**

The secondary and other endpoints will be analyzed using the same statistical methodology as for the primary efficacy endpoint (except for weight and waist circumference).

### **13.8 Safety Analysis**

For this morbidity/mortality trial, a benefit risk assessment is important. For this purpose safety analyses will be conducted on the same population (ITT) and using the same evaluation period as for efficacy analyses. (ie, from randomization until study end date)



### **13.8.1 Adverse Events**

#### **13.8.1.1 Definitions**

All adverse events recorded during the study will be coded according to Medical Dictionary for Regulatory Activities.

#### **13.8.1.2 Adverse Events**

Summaries will be done for the following types of AE:

- Number (%) of participants with any AE,
- Number (%) of participants with any new pulmonary condition,
- Number (%) of participants with any cardiology and neurologic
- Number (%) of participants permanently withdrawn from treatment.

All summaries will display, by treatment group, the overall frequency of participants with events, the frequency of participants with events within each primary system organ class and by preferred terms. For each preferred term and each system organ class a patient will be counted only once. For summaries on severe or medical device-related AE, for a given patient, the highest severity or relationship for a specific preferred term will be considered.

#### **13.8.1.3 Deaths and Serious Adverse Events**

Serious adverse events and events leading to death will be summarized overall and by primary system organ class and preferred term.

#### **13.8.1.4 Adverse Events Leading to Treatment Discontinuation**

Adverse events leading to treatment discontinuation will be summarized overall and by primary system organ class and preferred term.

### **13.8.2 Clinical Laboratory Evaluations**



Not Applicable in this Clinical Trial.

Descriptive statistics will also be used to summarize the values and changes from baseline for each treatment group across time.

### **13.8.3 Vital Signs**

Vital signs need to be within normal parameters for age of participant and remain so for the 21 day period of the trial. Vitals shall be taken before trial enrollment by prescribing physician.

## **14. SUBSTUDIES**

Not Applicable in this Clinical Trial.

## **15. ETHICAL AND REGULATORY STANDARDS**

### **15.1 Ethical Principles**

This Clinical Trial will be conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies, and the ICH guidelines for Good Clinical Practice (GCP). Those Investigators participating as leaders in this trial, including members of the Executive and Operations Committees and National Coordinators, will receive compensation for their time but will receive no financial profit from their activities related to the trial.

### **15.2 Laws and Regulations**

This Clinical Trial will be conducted in compliance with all international laws and regulations, and national laws and regulations of the countries in which the clinical trial is performed, as well as any applicable guidelines. The trial will be registered on [www.clintrials.gov](http://www.clintrials.gov) and on other sites, as appropriate.



### **15.3 Informed Consent**

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, and under the Investigator's responsibility, should fully inform the patient of all pertinent aspects of the clinical trial, including the written information given approval/favorable opinion by the Institutional Review Board/Ethics Committee (IRB/EC).

Prior to a participant's participation in the clinical trial, the written Informed Consent Form should be signed, name filled in and personally dated by the patient or by the participant's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written Informed Consent Form will be provided to the patient.

If informed consent is obtained under special circumstances (emergency, from a guardian, minor, etc.), the method should be specified following the ICH requirements. The first part of the section should be adapted, keeping the point as appropriate.

The Informed Consent Form used by the Investigator for obtaining the participant's informed consent must be reviewed and approved by the Sponsor prior to submission to the appropriate IRB/EC for approval/favorable opinion.

### **15.4 Institutional Review Board/Independent Ethics Committee (IRB/EC)**

In this Phase IV, clinical trial for efficacy of previously cleared device under current FDA 510k indications and no new indications being investigated the need for an IRB/EC is not required by law or by ICH GCP guidelines.

If the Sponsor chooses to enlist the services of an IRB/EC then:

The Investigator must submit this Clinical Trial Protocol to the appropriate IRB/EC, and is required to forward to the Sponsor a copy of the written and dated approval/favorable opinion signed by the Chairman with IRB/EC composition.

The Clinical Trial (study number, Clinical Trial Protocol title and version number), the documents reviewed (Clinical Trial Protocol, Informed Consent Form, Investigator's Brochure, Investigator's CV, etc.) and the date of the review should be clearly stated on the written IRB/EC approval/favorable opinion.



Investigational Product will not be released at the study site and the Clinical Trial will not start until a copy of this written and dated approval/favorable opinion has been received by the Sponsor.

During the Clinical Trial, any amendment or modification to the Clinical Trial Protocol should be submitted to the IRB/EC. It should also be informed of any event likely to affect the safety of participants or the continued conduct of the Clinical Trial, in particular any change in safety. All updates to the Investigator's Brochure will be sent to the IRB/EC.

If requested, a progress report is sent to the IRB/EC annually and a summary of the Clinical Trial's outcome at the end of the Clinical Trial.

## **16. STUDY MONITORING**

### **16.1 Responsibilities of the Investigator(s)**

The Investigator(s) undertake(s) to perform the Clinical Trial in accordance with this Clinical Trial Protocol, ICH guidelines for Good Clinical Practice and the applicable regulatory requirements.

The Investigator is required to ensure compliance with all procedures required by the Clinical Trial Protocol and by study procedures provided by the Sponsor (including security rules). The Investigator agrees to provide reliable data and all information requested by the Clinical Trial Protocol (with the help of the Case Report Form [CRF], Discrepancy Resolution Form [DRF] or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents to Sponsor representatives.

If any particular circuits have to be defined (e.g., e-CRF, Email), particular attention should be paid to the confidentiality of the participant's data to be transferred.

The Investigator may appoint such other individuals as he/she may deem appropriate as Sub-Investigators to assist in the conduct of the Clinical Trial in accordance with the Clinical Trial Protocol. All Sub-Investigators shall be timely appointed and listed. The Sub-Investigators will be supervised by and under the responsibility of the Investigator. The Investigator will provide them with a Clinical Trial Protocol and all necessary information.



## **16.2 Responsibilities of the Sponsor**

The Sponsor of this Clinical Trial is responsible to Health Authorities for taking all reasonable steps to ensure the proper conduct of the Clinical Trial Protocol as regards ethics, Clinical Trial Protocol compliance, integrity and validity of the data recorded on the Case Report Forms. Thus, the main duty of the Monitoring Team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the Clinical Trial.

At regular intervals during the Clinical Trial, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the Monitoring Team to review study progress, Investigator and patient compliance with Clinical Trial Protocol requirements, and any emergent problems. During these monitoring visits, the following but not exhaustive list of points will be scrutinized with the Investigator: patient informed consent, patient recruitment and follow-up, Serious Adverse Event documentation and reporting, outcome events documentation and reporting, Investigational Product allocation, patient compliance with the Investigational Product regimen, Investigational Product accountability, concomitant therapy use and quality of data.

## **16.3 Source Document Requirements**

According to the ICH guidelines for Good Clinical Practice, the Monitoring Team must check the Case Report Form entries against the source documents, except for the pre-identified source data directly recorded in the Case Report Form. The Informed Consent Form will include a statement by which the patient allows the Sponsor's duly authorized personnel, the Ethics Committee (IRB/EC), and the regulatory authorities to have direct access to source data which supports the data on the Case Report Forms (e.g., participant's medical file, appointment books, original laboratory records, etc.). These personnel, bound by professional secrecy, must keep confidential all personal identity or personal medical information (according to confidentiality rules).

## **16.4 Use and Completion of Case Report Forms and Additional Requests**

It is the responsibility of the Investigator to maintain adequate and accurate CRFs designed by the Sponsor to record all observations and other data pertinent to the clinical investigation. All CRFs should be completed in their entirety in a neat, legible manner to ensure accurate



interpretation of data; a black ball point pen should be used to ensure the clarity of the reproduced copy of all CRFs, which should be emailed within 48 hours of completion or any modification to the Central Database number.

Should a correction be made, the information to be modified must not be overwritten. The corrected information will be transcribed by the authorized person next to the previous value, initialed and dated, and the corrected CRF should be emailed again to the Central Database number.

The computerized handling of the data by the Sponsor after receipt of the CRFs may generate additional requests (DRF) to which the Investigator is obliged to respond by confirming or modifying the data questioned. Unresolved requests will be emailed to the Investigator at least every 2 weeks. Modified CRFs following resolution of the queries should be emailed again to the Central Database number.

## **17. ADMINISTRATIVE RULES**

### **17.1 Curriculum Vitae**

An updated copy of the curriculum vitae limited to the experience, qualification and training for each Investigator and Sub-Investigator will be provided to the Sponsor prior to the beginning of the Clinical Trial.

### **17.2 Record Retention at Study Site(s)**

The Investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents. All data and information shall be kept in secure digital format with no paper files stored. Data drives shall all be taken offline and physically retained in triple level secure vault. These data records shall be available for inspection by any and all Federal regulatory agencies, State agencies or parties legally designated by the Sponsor within two (2) business days. Records shall be available during normal business hours, during normal business days with the exception of weekends or any bank holidays.

It is recommended that the Investigator retain the study documents at least fifteen (15) years after the completion or discontinuation of the Clinical Trial.



However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

The Investigator must notify the Sponsor prior to destroying any study essential documents within the fifteen (15) year period following the Clinical Trial completion or discontinuation.

If the Investigator's personal situation is such that archiving can no longer be ensured by him/her, the Investigator shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

## **18. CONFIDENTIALITY**

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the Clinical Trial, including, but not limited to, the Clinical Trial Protocol, the CRFs, the Investigator's Brochure and the results obtained during the course of the Clinical Trial, is confidential. The Investigator or any person under his/her authority agrees to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

However, the submission of this Clinical Trial Protocol and other necessary documentation to the Ethics Committee (IRB/EC) is expressly permitted, the IRB/EC members having the same obligation of confidentiality.

The Sub-Investigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Sub-Investigators of the confidential nature of the Clinical Trial.

The Investigator and the Sub-Investigators shall use the information solely for the purposes of the Clinical Trial, to the exclusion of any use for their own or for a third party's account.

## **19. PROPERTY RIGHTS**

All information, documents and Investigational Product provided by the Sponsor or its designee are and remain the sole property of the Sponsor.



The Investigator shall not mention any information or the Product in any application for a patent or for any other intellectual property rights.

All the results, data, documents and inventions, which arise directly or indirectly from the Clinical Trial in any form, shall be the immediate and exclusive property of the Sponsor. The complete verified database will be shared with the Operations Committee, which shall have full access to all data.

The Sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The Sponsor shall be under no obligation to patent, develop, market or otherwise use the results of the Clinical Trial.

As the case may be, the Investigator and/or the Sub-Investigators shall provide all assistance required by the Sponsor, at the Sponsor's expense, for obtaining and defending any patent, including signature of legal documents.

## **20. DATA PROTECTION**

- The participant's personal data and Investigator's personal data which may be included in the Sponsor database shall be treated in compliance with all applicable laws and regulations;
- When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

## **21. INSURANCE COMPENSATION**

The Sponsor certifies that it has taken out a liability insurance policy that covers the liability of the medical device. This insurance policy is in accordance with local laws and requirements. An insurance certificate will be provided to the Investigator in countries requiring this document. The insurance of the Sponsor does not relieve the Investigator and the collaborators of any



obligation to maintain their own liability insurance policy as required by applicable law.

## **22. SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES**

For the purpose of ensuring compliance with the Clinical Trial Protocol, Good Clinical Practice and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the Sponsor and inspection by applicable regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that this personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator is notified of a future inspection by the authorities, he will inform the Sponsor and authorize the Sponsor to participate in this inspection.

The confidentiality of the data verified and the protection of the should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

## **23. PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT SITE**

### **23.1 Decided by the Sponsor in the Following Cases:**

- In the event the results of the Clinical Trial do not appear to be scientifically convincing to the Sponsor;
- If the aim of the Clinical Trial has become outdated or is no longer of interest;
- If the information on the product leads to doubt as to the benefit/risk ratio;



- If the Investigator has received from the Sponsor all Investigational Product, means and information necessary to perform the Clinical Trial and has not included any patient after a reasonable period of time mutually agreed upon;
- In the event of breach by the Investigator of a fundamental obligation under this agreement, including but not limited to breach of the Clinical Trial Protocol, breach of the applicable laws and regulations or breach of the ICH guidelines for GCP;
- If the total number of participants are included earlier than expected;  
In any case the Sponsor will notify the Investigator of its decision by written notice.

### **23.2 Decided by the Investigator**

The Investigator must notify (30 days' prior notice) the Sponsor of his/her decision and give the reason in writing.

In all cases (decided by the sponsor or by the Investigator), the appropriate Ethics Committee(s) (IRB/EC) and Health Authorities should be informed.

## **24. CLINICAL TRIAL RESULTS**

- The Sponsor will be responsible for preparing a Clinical Study Report;
- When the data from all investigational sites have been fully analyzed by the Sponsor, the latter will communicate the results of the Clinical Trial to the Investigator(s).

## **25. PUBLICATIONS AND COMMUNICATIONS**

It is the policy of the Sponsor to encourage the presentation and/or publication of the results of



their studies, using only clean, checked and validated data in order to ensure the accuracy of the results.

At least thirty (30) days in advance of proposed submission, the primary author should forward a copy of the manuscript or abstract for review by the Sponsor, and, if necessary, delay publication or communication for a limited time in order to protect the confidentiality or proprietary nature of any information contained therein.

The Sponsor may also request that the Sponsor's name and/or names of one or several of its employees appear or not appear in such publication.

In multi-center studies conducted by an Executive Committee, with an Operations Committee, it is those bodies that are responsible for presentations and/or publications. The Committee must send a copy of the manuscript or abstract to the Sponsor for review at least thirty (30) days before submission.

All study participants (Investigators and Committee members) give full authority to the Executive Committee for primary presentation and/or primary publication of the results in the name of wholehearted collaborators. No other publication is allowed before the primary publication. Any subsequent presentation or publication by a study participant (including for sub-studies) must be approved by the Operations Committee and make reference to the study and the primary publication. The final decision to publish articles and their content will be made by the Operations Committee after prior notice to the Sponsor, allowing their review and comments on all manuscripts (at least thirty days in advance of submission, unless a mutual agreement allows a shorter notice).

## **26. CLINICAL TRIAL PROTOCOL AMENDMENTS**

All appendices attached hereto and referred to herein are made part of this Clinical Trial Protocol.

The Investigator should not implement any deviation from, or changes of the Clinical Trial Protocol without agreement by the sponsor and prior review and documented approval/ favorable opinion from the IRB/EC of an amendment, except where necessary to eliminate an immediate hazard(s) to clinical trial participants, or when the change(s) involves only logistical



or administrative aspects of the trial. Any change agreed upon will be recorded in writing, the written amendment will be signed by the Investigator and by the Sponsor and the signed amendment will be filed with this Clinical Trial Protocol.

Any amendment to the Clinical Trial Protocol requires written approval/favorable opinion by the IRB/EC prior to its implementation, unless there are overriding safety reasons.

In some instances, an amendment may require a change to the Informed Consent Form. The Investigator must receive an IRB/EC approval/favorable opinion concerning the revised Informed Consent Form prior to implementation of the change.

## **27. BIBLIOGRAPHIC REFERENCES**

Please see User Manual

## **28. APPENDICES**

### **Appendix 1: The Optional Study Group Coordinating Center and Study Sponsor Responsibilities**

#### **1. Optional Study Group Project Team responsibilities**

The Optional Study Group 2, is independent of the Sponsor and its primary function is to facilitate and oversee the execution of the study in collaboration with the Sponsor. The Optional Study Group Project Office will keep the Operations Committee apprised of the progress and conduct of the trial and will provide ongoing administrative support to the Clinical Events Committee and other committees.

Key members of the Optional Study Group Project Team are:

- Oversight activities of the Optional Study Group Project Team include the following:
- Coordination of protocol and CRF review at the Optional Study Group Site Management for US sites.
- Review of monitoring visit reports (selection, initiation and interim reports)



- Direct communication with the sites regarding the trial and any relevant issues (calls documented in a database)
- Re-training of sites staff in case of turnover
- Distribution of a monthly newsletter
- Maintenance of a hot-line service for medical questions, including medical advice if unblinding is considered

#### Clinical Events Committee (CEC):

- Development of CEC review forms and CEC review instructions
- Appointment of medical reviewers blinded to treatment at Optional Study Group for validation of events reported in English (approximately 50% of adjudicated events)
- Appointment of decentralized physician reviewers in each of the non-English languages
- Coordination of the ongoing medical review of adjudicated endpoints
- Reviews contracts and payments

#### Executive Committee, Operations Committee and National Coordinators:

- Coordination, organization of meetings, distribution of documents and minutes
- Contracts and honorarium payments

#### DMC:

- Support for organization of DMC meetings
- Contracts and honorarium payments Prepare final study manuscript for publication



## 2. Study Sponsor responsibilities

The Study is being sponsored by Med Systems, Inc., LTD., and monitored by Med Systems, Inc., LTD.. As such, they will share legal and regulatory responsibilities for the conduct of the study and control and distribution of the investigational device, Electro Flo 5000 . In fulfilling these responsibilities according to Med Systems, Inc., LTD. standard operating procedures, the Sponsor's activities include the following:

- Medical Input
  - Participate at the Operations Committee and the Executive Committee meetings or teleconferences
  - Update the Clinical Investigator's Brochure at least annually
- Medical Device Supplies
  - Manufacture and ship medical devices and matching-placebos
  - Release medical device supplies to individual Clinical Centers after receipt of documentation at the Sponsor's regional centers
- Funding
  - Provide indemnification letters as required
  - Provide funding and contracting with Investigators for the conduct of the study.
- Regulatory
  - Obtain all necessary documents from Investigators for regulatory filings



- Ensure initial, and then annual (when applicable) IRB/EC approval is obtained by Investigators
- Monitor compliance with all applicable national and local law maintain and coordinate contact with national regulatory authorities
- Submit all necessary regulatory filings oversee all communication between DMC and regulatory authorities to make certain it occurs in a timely manner
- Perform all statistical analysis and medical writing of clinical reports for
- Registration applications
- Study Monitoring
  - Develop a study monitoring plan
  - Monitor clinical centers
  - Ensure protocol adherence
  - Assess timely completion and submission of Case Report Forms (CRFs) and support documents
  - Monitor quality and homogeneity of all data processing activities
  - Quality Assurance audits of the study as needed
  - Monitoring and overseeing the maintenance of study conduct according to ICH, GCPs, and all country-specific regulations
  - Clarify queries or missing documents, including assisting Optional Study Group Project Team to
  - Clarify queries or missing documents from US sites maintain necessary communication with all National Coordinators, Investigators and study personnel
- Data Management and Study Medical device Allocation Procedure



- Develop and manage the Central Study Database, perform data entry and validate records in the email acquisition system
- Implement appropriate measures for data quality control
- Implement and manage the central randomization system
- Generate patient visit schedules for all centers compile and
- Generate weekly study status reports for general distribution to all personnel involved in the study, centrally and locally Study Archives
- Maintain study archives Study Reporting provide support to the Executive Committee for the primary scientific publication of the study
- Develop a clinical study report for registration purpose

## Responsibilities

## Membership

Expert members: Function Chairman Member/International PI Member/Investigator

## **Appendix 2: The Executive Committee**

The Executive Committee is composed of university-based and Sponsor-based scientists with clinical and methodological expertise. The committee has the overall responsibility for producing and conducting a scientifically sound study and ensuring accurate reporting of the study. In that capacity, the Executive Committee must address and resolve scientific issues encountered during the study. This committee will meet at least twice a year.

All proposed ancillary research investigations on participants enrolled must be approved by the Executive Committee. The primary scientific publication reporting the study results is the responsibility of the Executive Committee. Collaborating Investigators or members of the various study committees wishing to prepare secondary publications must submit proposals and manuscripts to the Executive for approval. The Sponsor reserves the right to review manuscripts prior to submission for publication in a scientific journal. The final decision on all publications will be the responsibility of the Operations Committee.



## Responsibilities

### **Appendix 3: The Operations Committee**

The Operations Committee is responsible for ensuring that study execution and management are of the highest quality. Issues relating to regulatory reporting are the responsibility of the Sponsor, although the Operations Committee is to be kept informed of these activities. The Operations Committee will determine its own guidelines and approve the criteria and guidelines of the other committees prior to commencement of the study. The Operations Committee will be responsible for publications.

The Operations Committee will convene regularly to discuss and report on the ongoing supervision of the study.

## Membership

## Working procedure

The Operations Committee will need to determine its own working guidelines, especially regarding the decision-making process on specific aspects of the study conduct.

### **Appendix 4: The Clinical Events Committee (CEC)**

## Responsibilities

The Clinical Events Committee is charged with the responsibility for validating all reported primary efficacy outcomes and validating the classification of the cause of all deaths. The event adjudication process will be coordinated by C5.

Members of the Clinical Event Committee will be chosen based on their clinical expertise and language skills. Adjudicators will be trained at a preliminary meeting where study definitions will be reviewed and test cases performed to ensure uniform application of study definitions. Reported events will be adjudicated by at least one committee member. Dossiers of reported events will be prepared and distributed to committee members on a regular basis to ensure that events are adjudicated in a timely fashion. Each committee member will be requested to review the dossiers sent to him/her and acknowledge in writing his/her agreement/disagreement with the investigator's interpretation of events.

## **Definitions for Validation of Reported Outcome Events**



Reported outcome events are all defined in the protocol.

### **Review Process for Reported Efficacy Outcome Events**

- First adjudicator agrees with Investigator's report of outcome event:
  - Agreement acknowledged in writing and filed at Optional Study Group
  - Event Adjudication database updated accordingly
  - Investigator's report of outcome event accepted
  - Adjudication complete
- First adjudicator disagrees with Investigator's report of outcome event:
  - Disagreement or uncertainty acknowledged in writing
  - Event Adjudication database updated accordingly
  - Outcome event forwarded for review to second adjudicator who is unaware of prior adjudication
- If second adjudicator agrees with Investigator's report of outcome event:



- Agreement acknowledged in writing and adjudication report filed at Optional Study Group
  - Event Adjudication database updated accordingly
  - Investigator' s report of outcome event accepted
  - Adjudication complete
- If second adjudicator disagrees with Investigator's report of outcome event and agrees with first adjudicator:
  - Disagreement acknowledged in writing and adjudication report filed at Optional Study Group
  - Event Adjudication database updated accordingly
  - Adjudicator' s report of outcome event accepted
  - Adjudication complete
- If second adjudicator is uncertain:



- Stalemate acknowledged in writing
- Event Adjudication database updated accordingly
- Outcome event forwarded to Chairman of Clinical Events Committee for resolution. Final decision mandatory at this stage
- Chairman's decision acknowledged in writing and reports filed at Optional Study Group  
Adjudication complete

The Clinical Events Committee and Optional Study Group will establish detailed written guidelines for the event adjudication process. The CEC will prepare a manual that will describe the quality assurance procedures.

The Clinical Events Committee will meet initially for orientation and training. Afterwards, meetings will be held as required to address and resolve committee policy issues.

## **Membership**

Chairman :

Members will be supplemented as necessary in order to ensure that two cardiologists and two neurologists are available to represent most languages of study participant countries.

## **General Overview**

### **Appendix 5: The Data Monitoring Committee (DMC)**

The Study will be conducted in a double-blind manner in which participants and treating physicians are blinded. The trial management team, including Operations Committee, Executive Committee, Clinical Events Committee, the Optional Study Group Project Team and the Sponsor will also be blinded with respect to treatment allocation.

To facilitate its responsibilities, the DMC will have an Associated Statistician who will receive study data directly from the Central Database and who will remain independent of the trial



management team. The DMC Associated Statistician is not a member of the DMC, but presents data to the committee and is responsible to the Chairman.

The DMC Associated Statistician, being unblinded, will not be able to edit/alter any part of the Central Database.

Other than the Associated Statistician, routine access to the treatment code will be restricted to the Chairman of the DMC, except for emergency unblinding on a case-by- case basis, if required for regulatory purpose.

### **DMC Responsibilities**

Primary:

1. Regular review of safety data including serious adverse events, as defined in the DMC Charter

2. Feedback to the Chairman of the Operations Committee Secondary:

- A. Respond to special requests from regulatory authorities or IRB/ECs

- B. Recommendations for protocol amendments

Verification of final analysis of the study will be done by the DMC Associated Statistician.

### **Safety Review**

Recommendation to stop a trial early for safety reasons is, by definition, a subjective judgment. The DMC is composed of eminent clinicians and methodologists who are experienced with clinical trials and can be relied upon to exercise good judgment in weighing the potential risks and benefits to participants as data accumulate in this trial.

The DMC will fulfill its responsibility to monitor the safety of participants by conducting formal reviews of accumulated safety and efficacy data. These reviews will normally occur at regular intervals as defined in the DMC charter, however, in case of specific concerns, ad-hoc meetings can be set up. The DMC Associated Statistician will prepare a report of aggregate data



summaries and other data, where appropriate, for each treatment group. This report will be circulated to each member of the DMC at least one week prior to their collective review. The committee will then convene, either by face-to-face meeting or by telephone conference call, to make its recommendation to the Operations Committee with respect to continuance of the trial or any changes to the conduct of the trial. A formal written communication to the Chairman of the Operations Committee will then follow. Minutes of all official meetings of the DMC and any recommendations will ultimately be part of the Sponsor's master files after the study is over and the results are known (archives).

The report of data summaries and listings will include information on both safety and efficacy parameters, together with status reports designed to show the extent to which the trial is being executed according to protocol. Included among the safety data will be (a) all deaths (b) SAEs and (c) other adverse events as requested by the DMC. Efficacy summaries will provide information on the occurrence of all study outcomes. The outcome events are considered as distinct from adverse events and summarized separately. At each review by the DMC, consideration of a decision to stop the trial on grounds of patient safety will weigh the current evidence of differences between treatments regarding adverse effects (as expressed by mortality, adverse event reports, etc) against emerging trends in efficacy. Providing efficacy data at each of these routine safety reviews does not constitute a formal interim analysis of efficacy, and these analyses will not, in and of themselves, be used for stopping the trial (see next section).

Data for the safety review will be made available from the Central Database on a quarterly basis (roughly three weeks prior to DMC meetings). Serious adverse events are required to be reported rapidly to the Sponsor and will be entered into a separate Pharmacovigilance database that will also be transferred to the DMC Associated Statistician, in addition to the Central Database. Primary outcome events will be reviewed by the Clinical Events Committee on an ongoing basis to determine if each reported event meets the defined criteria for a study outcome event. The DMC will review data on all reported outcome events. Additional summaries will show the results of the Clinical Event Committee's judgments on the subset of reports that has been reviewed by this committee.

### **Feedback From the DMC**

#### **a) To the Operations Committee**

All communications between the Operations Committee and the DMC will be through the office of the Chairman of the Operations Committee and be documented in writing.



Information provided by the DMC may be confidential and must be kept so within the Operations Committee.

The Operations Committee may request supplementary information from the DMC, if necessary. The DMC Chairman will consider all such requests.

#### b) To/From the Sponsor

Special requests from any national regulatory authority requiring DMC input will be forwarded by the Sponsor to the Chairman of the Operations Committee. Any requests that cannot be performed by the Chairman of the Operations Committee will be forwarded to the Chairman of the DMC to be done by the DMC Associated Statistician. New preclinical and clinical information from other trials will be provided to the DMC in an updated Investigator's Brochure.

Representatives of the study organization will discuss the content and timing of such feedback with the agencies concerned. All necessary analyses and reports will be sent in a timely fashion. The Chairman of the Operations Committee and the Sponsor's regulatory department will be copied on the covering letter to any reports provided to individual regulatory agencies. However, no unblinded reports will be sent to any organization other than the regulatory agency that requested it.

### **Protocol Change Recommendations**

It is possible that the DMC might suggest changes in the protocol as a result of their reviews. Any suggestions will be provided in writing to the Chairman of the Operations Committee, including a detailed rationale with the anticipated consequences in terms of study bias.

### **Confidentiality**

Information provided to the DMC is strictly confidential and must not be disclosed other than through the mechanisms described above. In particular, members of the DMC cannot publish any information derived from its privileged access to the study data without the approval of the Operations Committee.

### **Membership**

Chairman Members

Independent Statistician