Identify the Epidural Space with EpiFaith™ Syringe in Air and Saline based Procedures

Short Title: EpiFaith™ Syringe for Epidural Space Detection

Indication: Epidural space localization

Protocol Number: EPS01

Version/Date: **3.0/ March 15, 2019**

Study Site: Taipei Veterans General Hospital

Sponsor: Flat Medical Co., Ltd.

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Objective:

Clinical Study Protocol

I have read the protocol and agree to conduct this clinical study in accordance with all stipulations of the protocol, with applicable law and regulations and in accordance with the ethical principles outlined in the Declaration of Helsinki.

Principal Investigator:

Chien-Kun Ting, M.D., Ph. D.

Taipei Veterans General Hospital

Date

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Flat Medical Co., Ltd. **Date**

SYNOPSIS

I. Protocol Title:

Identify the Epidural Space with EpiFaith^{TM} Syringe in Air and Saline based Procedures.

II. Objectives:

The objective of the study is to **verify the efficacies of both** air and saline based procedure of EpiFaith syringe for assisting the **needle** localization of the epidural space.

III. Test device:

1. Name: EpiFaith syringe
2. Manufacturer: Flat Medical Co., Ltd.
3. Method of use: EpiFaith Syringe can provide a visual signal to assist anesthesiologists to localize the epidural space.
4. Device category: Class II

IV. Study design:

1. ■ Controlled: ■ Same device
   ☐ other:
   ☐ Uncontrolled
2. Blinding ☐ Open label ☐ Evaluator blind ■ Single blind
   ☐ Double blind ☐ Double dummy ☐ Other
3. Randomized: ■ Yes ☐ No
4. ■ Parallel ☐ Cross-over ☐ Other
5. Duration of treatment: 30 minutes
6. Titration: ☐ Forced ☐ Optional ■ None
7. ☐ Multi-national ☐ Multi-center (Taiwan) ■ Single center

V. Endpoints:

1. Primary Endpoint(s):
   - Success of epidural localization
2. Secondary Endpoints
   - Time to identify the epidural space
   - Duration of the epidural space localization procedure
   - Number of attempts
   - Number of the occurrence of false positive
   - The distance from the skin to the epidural space
   - Number of change insertion segment

VI. Selection criteria:

- **Main Inclusion Criteria**
  1. 20 years and older
  2. Surgery requiring epidural anesthesia or analgesia
  3. ASA Physical Status 1 to 3
- **Exclusion Criteria**
  1. Bleeding and clotting disorders
     - Platelet count < 100,000 / mm^3
     - International normalized ratio (INR) > 1.5
  2. History of peripheral neuropathy
  3. Neuromuscular or neuropsychiatric disease
  4. Marked spinal deformities or a history of spinal instrumentation
  5. Systemic infection
  6. Skin infection at the injection site
  7. Significant heart failure, e.g. New York Heart Association (NYHA) Functional Classification 3 or 4

VII. Study procedures:

This is a single blind, randomized study. Subjects who will receive a surgery requiring epidural anesthesia or analgesia and meet all of the study criteria will be enrolled in the study. All subjects must sign an informed consent and receive a copy of the signed and dated informed consent form prior to participation in the trial.

The study consists of 2 study visits: Visit 1 (Screening Visit) and Visit 2 (Operative Visit). After screening, eligible subject will be randomly assigned to one of the following groups: Group A: detection by EpiFaith syringe with air; Group S: detection by EpiFaith syringe with saline with a 1:1 ratio. In Visit 2, the following variables will be recorded and rated during the process of epidural space localization: Success of epidural localization, time to identify the epidural space, duration of the epidural space localization procedure, number of attempts, Number of the occurrence of false positive, the distance from the skin to the epidural space, and number of change insertion segment. Adverse events and concomitant treatments will be also recorded.

VIII. Concomitant therapy:

1. Prohibited therapy:

The following medications are prohibited within 5 days prior to epidural localization:

- **Anti-coagulants (e.g., Warfarin, Heparin, Plavix)**
- **Antiplatelet**

2. All concomitant therapies related to epidural localization should be recorded, including AE treatment.

IX. Statistics:

1. Primary hypothesis: ☐ Superiority ☐ Non-inferiority ☐ Equivalence ■ Other

2. Sample size:

Considering the recommendation given by Lancaster, Dodd &Williamson. A total of 60 subjects (30 subjects per group) will be required in this study to obtain parameters such as ratio, mean and standard deviation which will be used in a sample size calculation for the full-scale trial, and to estimate the rate of participants who drop out of the trial.

3. Efficacy population: ■ITT □PP □Other

Safety population: □ITT □PP ■Other

4. Statistical method(s) for efficacy/safety evaluations:

Statistical analyses will be reported using summary tables, graphs, and data listings. Analysis are performed with SPSS, Version 20.0 (IBM Corporation, Armonk, NY, USA). The analysis population will be summarized by A and S groups. For categorical variables, frequencies and percentages will be summarized; continuous data will be shown as descriptive statistics. The variables within a normal distribution will be compared using Student's t-tests, and those without a normal distribution will be compared using the Mann-Whitney U test. The number of patients will be compared between the groups using the Fisher's exact test. All information will be summarized and presented in statistical analysis tables. As for data of efficacy and safety variables, no imputation method is applied.

Incidence of the adverse events will be summarized. In the case of CTCAE grade summaries, the most severe event will be presented in summary tables in the case of multiple occurrences per patient. The frequency and the percentage of each category will be presented. All safety parameters, including adverse events, adverse device effect, serious adverse event, serious adverse device effects and unanticipated adverse device effect will be listed by A and S groups. The Medical Dictionary for Regulatory Activities (MedDRA) adverse event dictionary will be used to map verbatim adverse events to preferred terms and system organ class. Fisher's exact test will be applied for comparing the incidences of adverse events between treatment groups.

5. Planned interim analysis: □Yes ■No

X. Schedule of Assessments

Procedures	**Screening(3)**	**Operative period**
	Visit 1	Visit 2
Informed Consent	X	
Inclusion/Exclusion Criteria(1)	X	X
Medical History	X	
Demography	X	
Physical Examination	X	
Randomization		X
Epidural Space Localization Planning		X
Epidural Space Localization with Study Test Device		X
Concomitant Therapy		X
Adverse Events(2)		X

(1): For exclusion criteria #1, platelet count and INR in admission medical record are acceptable.
(2): The AEs and SAEs will be recorded from the start to the end of epidural space localization.
(3): All activities listed for the Screening Visit should be accomplished prior to those listed in the Operative Visit.

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LIST OF ABBREVIATIONS

Abbreviations	Terms and Definitions
AE	Adverse Event
ADE	Adverse Device Effect
ARD	Acute Respiratory Disease
ASA	American Society of Anesthesiologists
CAD	Coronary Artery Disease
COPD	Chronic Obstructive Pulmonary Disease
CRA	Clinical Research Associate
CRF	Case Report Form
CVA	Cerebrovascular Accident
DIC	Disseminated Intravascular Coagulation
DM	Diabetes Mellitus
ES	Epidural space
ESRD	End-stage renal disease
GCP	Good Clinical Practice
HTN	Hypertension
ICH	International Conference of Harmonisation
LOR	Loss of resistance
MI	Myocardial infarction
PCA	Post Conceptional Age
SDE	Serious Adverse Event
TIA	Transient Ischemic Attack

1. INTRODUCTION

Locating the epidural space is an indispensable part of obstetrical analgesia, surgical anesthesia, postoperative analgesia, and chronic pain control.

The traditional method of locating the position of the needle tip is loss of resistance technique (i.e., the "LOR"), which is based on detecting the pressure drop occurring at the moment the needle tip reaching the epidural space. Because the pressure of the epidural space is lower than the cavities of others tissue, a free injection of air or liquid from the syringe can be induced, resulting in a sudden loss of resistance of the plunger. Thus, the anesthesiologist can detect the pressure drop by feeling the resistance of pushing the plunger of the attached syringe.

The epidural space is a very thin area near the spinal cord. The advance of needle must be stopped right after the needle tip reaches the epidural space to prevent accidental dural puncture, which may lead to cerebrospinal fluid leakage followed by intractable headache and injuries of the spinal nerves. However, the current incidence rates of accidental dural punctures are 0.19-3.6%[1].

Using the LOR hand feeling to locate epidural space relies on manual skill of the operator and the considerable experiences. Choosing air or saline for LOR technique depends on personal experiences of the operator. The variety of LOR techniques has increased the difficulty of learning[2].

Some objective and confirmatory devices based on LOR technique are developed, such as Episure and Epidrum, and have been discuss under clinical trial[3-5]. The results show a lower failure rate and a shorter time needed to identify the epidural space. However, the restriction of the media and the actuating pressure selection will deprive the anesthesiologists' habit.

The EpiFaith syringe is an improved LOR device with the ability to warn and help physicians to achieve the safe insertion is required. EpiFaith syringe provides objective, and quantitative pressure information as well as a visual signal which is triggered at the moment the needle tip enters the epidural space. Hence, the anesthesiologist can get a clear endpoint for the advancing of the needle easily. The advantages of EpiFaith syringe including that the anesthesiologist can control the epidural needle with both hands and achieve the real- time pressure detection.

The trial quantity of EpiFaith syringe were finished, as well as the biocompatibility testing to ISO 10993, the connector testing to ISO80369-7, epidural simulated testing on ex-vivo and in-vivo porcine spine were performed. Results of testing demonstrate that the EpiFaith syringe meets its performance specifications and is safe and effective for its intended use.

The aim of this study is to evaluate using the EpiFaith syringe with two different sensing medians for epidural localization. The hypothesis of the study is that EpiFaith syringe can detect LOR of epidural space effectively with its achievable pressure. It is beneficial to both junior and senior physicians by transforming the process into a safe and convenient procedure.

2. OBJECTIVE

The objective of the study is to verify the efficacies of both air and saline based procedure of EpiFaith syringe for assisting the needle localization of the epidural space.

3. STUDY DESIGN

3.1. Overall Study Design

This is a single blind, randomized study. Subjects who will receive a surgery requiring combined spinal -epidural technique and meet all of the study criteria will be enrolled in the study. All subjects must sign an informed consent and receive a copy of the signed and dated informed consent form prior to participation in the trial.

The study consists of 2 study visits: Visit 1 (Screening Visit) and Visit 2 (Operative Visit). After screening, eligible subject will be randomly assigned to one of the following groups: Group A: detection by EpiFaith syringe with air, or Group S: detection by EpiFaith syringe with saline with a 1:1 ratio. In Visit 2, the following variables will be recorded and rated during the process of epidural space localization: Success of epidural localization, time to identify the epidural space, duration of the epidural space localization procedure, number of attempts, Number of the occurrence of false positive, the distance from the skin to the epidural space, and number of change insertion segment. Adverse events and concomitant treatments will be also recorded.

3.2. Study Population

3.2.1. Subject number

Recruitment will stop when approximately 60 subjects are included.

3.2.2. Inclusion criteria

Subjects meeting all of the following criteria will be considered for enrollment into the study:

1. 20 years and older

2. Surgery requiring epidural anesthesia or analgesia
3. ASA Physical Status 1 to 3

3.2.3. Exclusion criteria

Subjects who meet any of the following criteria will be not enrolled in the study:

1. Bleeding and clotting disorders
   - Platelet count < 100,000 / mm^3
   - International normalized ratio (INR) > 1.5
2. History of peripheral neuropathy
3. Neuromuscular or neuropsychiatric disease
4. Marked spinal deformities or a history of spinal instrumentation
5. Systemic infection
6. Skin infection at the injection site
7. Significant heart failure, e.g. New York Heart Association (NYHA) Functional Classification 3 or 4

3.3. Withdrawal of Subjects from Therapy or Assessment

Each subject has the right to withdraw study at any time. In addition, the investigator may terminate a subject's participation from the study at any time if the investigator considers it necessary for any reason including:

- Consent withdrawn

The reasons for withdrawal will be recorded in the CRF.

3.4. Method of Assigning Subjects to Treatment Groups

Subjects will be randomized to one of the two groups (A group – EpiFaith syringe with air or S group – EpiFaith syringe with saline) at the ratio of 1:1. The randomization method will result in sealed, opaque envelopes containing the computer- generated, random assignment. Randomization will occur in blocks so that blocks of equal numbers of subjects will be used to avoid potential runs of assignments. The randomization code will be generated specifically for each center.

Screening number will be assigned once subject signed the inform consent. Only eligible subjects at Visit 2 will receive a randomization number at randomization. The subject will receive the

corresponding test devices assigned in the randomization envelope according to the randomization number. The number will be maintained by the investigator throughout the study. For any reason that a subject withdraws from the study prematurely after the randomization, his/her randomization number will not be reused. The next eligible subject will receive the lowest available randomization number.

3.5. Blinding

In order to eliminate a potential for bias, all subjects will be blinded to their treatment assignment. The investigator and research staffs will not know the randomization assignment at the time of subject enrollment to ensure that they do not accidentally notify the patient of their assignment until anesthesia. At Visit 2, the investigator will be informed of the randomized treatment assignment from randomization envelops. Subjects will remain blinded to their treatment assignment during study period.

The treatment codes are not to be prematurely broken to subjects unless an emergency situation, when the appropriate management of the subject necessitated acknowledge of the treatment allocation occurs. In such cases, the sponsor will be notified immediately, and the date, time, and the reason for breaking the blind as well as the individual who breaks the code must be documented.

3.6. Concomitant Therapy

(1) Prohibited therapy:

The following medications are prohibited within 5 days prior to epidural localization:

- **Anti-coagulants (e.g., Warfarin, Heparin, Plavix)**
- **Antiplatelet**

(2) All concomitant therapies related to epidural space localization procedure, including AE treatment, should be recorded.

(3) Preoperative fasting is mandatory to reduce the risk of aspiration at least 6-8 hours prior to anesthesia, including solid and liquid food. Prescribed medications which be allowed by investigator should be to taken with a sip of water less than two hours prior to anesthesia unless otherwise directed.

4. TEST DEVICE

4.1. Detail of Test Device

4.1.1. Components and accessories

The schematic views of EpiFaith Syringe are shown in Figure 1. The components are listed in Table 1.

Figure 1. The schematic view of the EpiFaith Syringe with Luer slip connector.

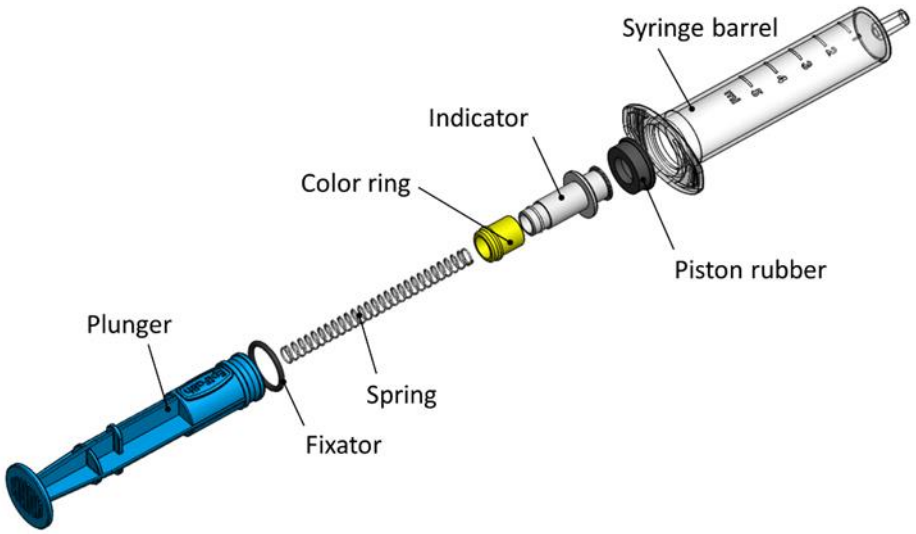

Figure 2. Explosion drawing of EpiFaith syringe

Table 1. Parts of EpiFaith Syringe

Parts of EpiFaith Syringe
Plunger
Spring
Indicator
Color ring
Fixator
Low friction rubber
Syringe barrel

The indicator, combined with a low friction rubber and a color ring, is connected to the plunger that allowing relatively co-axial movement of the two parts. The spring is placed inside the two parts. Decreasing the distance between the indicator and the plunger will compress the pre-load spring, as shown in Figure 2, leading to a spring force delivered to both indicator and the plunger. The relative position of the two parts is a result of force balance between the spring force and the pressure in the syringe, as principle described later. A fixator is attached to the plunger to increase the friction force between the plunger and the syringe barrel. The friction force can help to hold the position of the plunger without being moved by the spring force.

4.1.2. Detail description of the principle of EpiFaith Syringe

EpiFaith Syringe is based on the LOR technique, which means the visual signal is triggered by the pressure change occurring at the moment the needle tip arrives the epidural space.

EpiFaith Syringe should be connected to a 16-18 gauge epidural needle to locate the epidural space. After the needle is inserted to an appropriate depth and the stylet is removed, the EpiFaith Syringe can be connected to it. The initial pressure is induced by pushing the plunger and the fixator can hold the position of the plunger to maintain the pressure.

The spring is compressed due to the initial pressure and constantly delivers force to the content in the syringe (sensing material such as air or normal saline). Because of the spring force, the ejection of the sensing material will happen when the LOR occurring, resulting in the movement of the low friction rubber. It provides a visual signal to warn the anesthesiologists that the LOR has happened, which implies that the needle tip has arrives the epidural space. The parameters of the EpiFaith Syringe can be found in Figure 3.

For more detail please see the demo video: https://tinyurl.com/y8serflu

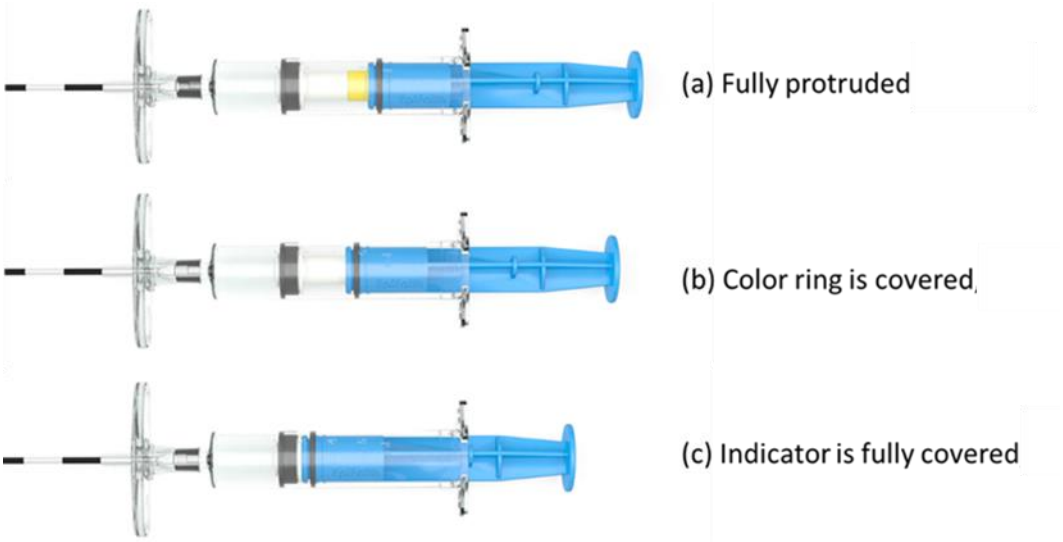

Figure 3. The different states of EpiFaith Syringe. (a) The indicator is fully protruded and the spring is released. (b)&(c) The spring is compressed and the indicator is covered by the plunger. The fixator can help to maintain the position of the rear plunger. Therefore, even though the spring constantly applies a spring force on both indicator and the plunger, the plunger will not be pushed back.

4.1.3. Use direction

All of the steps are performed under sterile conditions. The directions of using EpiFaith Syringe are shown in Figure 4.

EpiFaith™ syringe

Follow the instructions carefully.

INSTRUCTIONS FOR USE

Indications for use

The EpiFaith syringe is intended for use, in conjunction with an epidural needle, to verify the needle tip placement in the epidural space.

Intended performance

The loss of closed system pressure will trigger a warning signal, which is the movement of piston. The signal indicates that the needle tip has entered a body cavity or that the system is otherwise open. With physicians own experiences and skills, this product can be used as an aid that indicate whether the needle tip has entered the epidural space.

Contraindications and Restrictions on use

CAUTION

The product should only be used to aid the implement of loss of resistance technique and can only be used on patients that are suitable to the technique. This device must not be used unless the user has been adequately trained in the technique and is fully familiar with the user instructions, intended purpose, use and intended performance of this device.

Absolute contraindications include patient refusal, severe uncorrected hypovolemia, increased intracranial pressure, infection at the site of injection and known hypersensitivity to local anesthetics. Relative contraindications include coagulation disorders, anticoagulant therapy, pre-existing neurological disease, fixed cardiac output states, uncooperative patient, spine abnormalities or surgeries, and sepsis.

Risks

EpiFaith syringe is based on the loss of resistance technique. Thus, there is a risk, as with all epidural procedures performed with the technique, the performance of the device can be influenced by the conditions of the patient. The loss of resistance may not be obvious if the patient has abnormal pressure in epidural space or spinal anatomical abnormalities. Notice that a false signal may be given by the EpiFaith syringe if its contents leak into the tissues or if connections leak. Also, EpiFaith syringe may not give the warning signal if the needle is obstructed by tissue or blood.

Side effect

Side effects are limited to discomfort from subcutaneous bleeding and bruising from the needle entry point. There are no side effects directly attributable to the EpiFaith syringe.

Warnings

Do not use if packaging is damaged.
Do not re-use the product. Re-use of a single use product may lead to contamination and/or impairment of functional capability.
Do not re-sterilize.
Do not use after the expiry of the use by date of shelf life, which is located on the unit/ lot number label.
Do not withdraw the plunger out of the barrel, which may lead to contamination and/or impairment of functional capability.
The device is only made for loss of resistance technique. Do not use the product to deliver any kind of medicine.

Preparation and Assembly

General

The procedure should be carried out under the strictest sterile protocol.

Familiarization

It is essential that users familiarize themselves with the features and performance characteristics of the device. Please study the device and the user instructions carefully and do not proceed with a procedure until fully satisfied that the instructions are understood.

Environment and Safety

The procedures should be carried out in an appropriate anesthetic environment, having all emergency equipment and materials available, to ensure that the patient is safe.

Associated Consumables

Use the product with state of the art epidural kits, which have Luer/ NRFit connections.

CAUTION: The EpiFaith syringes are only compatible to state of the art 16-18G epidural needles with Luers / NRFits meet the standard ISO80369-7/-6.

Directions

CAUTION: Do not advance the needle if color ring is not covered.

1 Function test: Manual occluding and releasing to ensure the functional capability
CAUTION: The function of the EpiFaith syringe should be tested prior to use. Do not use the device and call the manufacturer if the function test failed.

a Fill the device with air by pulling the plunger. (Fig. 1a)

b Occluding the exit port, and then push the plunger until the color ring is covered and keep exit port occluded. If the color ring cannot remain covered, than the function test is failed. (Fig. 1b)

c Release the exit port. The piston should move forward rapidly. (Fig. 1c)

2 Fill EpiFaith syringe by pulling the plunger outwardly. (Fig. 2)
Note: EpiFaith syringe can be used with liquid or air.

3 Insert the needle through the tissue and anchored it in the appropriate region, such as ligamentum flavum. (Fig. 3)

4 Remove the stylet and attached the filled EpiFaith syringe to the needle. (Fig. 4)

5 Push the plunger slowly to start the pressure sensing. The color ring should be covered before advancing the needle. (Fig. 5)
Note: Pushing the plunger to cover the color ring and piston, an innerspring will be compressed to induce the pressure for LOR technique. The pressure is proportional to the covered level of the piston.
Note: Do not push the plunger if the piston shaft is entirely covered.
CAUTION: If the color ring cannot be covered after pushing the plunger, which implies the pressure fails to be built, consider whether the tip of the needle is already in the epidural space, in the sub-dural space or in the intrathecal space.

6 Advance the needle. (Fig. 6)
Note: This device can maintain the pressure automatically. Thus, it's not required to hold the plunger during advancing the needle. It is recommended to use both hands to control the needle and avoid pushing the plunger unless the contents have leaked.
Note: The content leaking is possible to occur if redirection of the needle is required. To avoid the leakage, we recommend to pull the plunger until the color ring is exposed before redirection. After the redirection, return to step 5 to complete the procedure.

7 Stop the needle advancing if the piston moves forward or the color ring appears, which implies the loss of resistance occurs. (Fig. 7)
CAUTION: As all loss of resistance technique, the loss of closed system pressure and the appearance of warning signal will indicate only that the needle tip has entered a void or that the system is otherwise open; hence, the user must rely on her/his own experience and carefully to confirm the location of the needle tip even if the warning signal occurs.

Storage

Store temperature between 10 - 35 °C.

Keep away from sunlight.

Disposal

Follow local protocols in respect of the disposal of the equipment.
Failure to dispose of the device correctly could lead to serious infections.
If an incorrect method of disposal is employed, the outcome may be harmful to a third party or to the environment.

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Figure 4. The use direction of EpiFaith Syringe

4.1.4. Associated consumables

Kit	Portex CSE Minipack

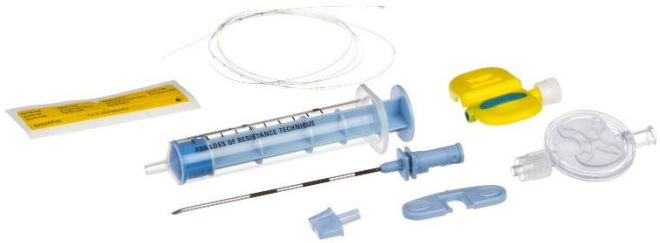

Figure 5. The associated consumables of this study

4.1.5. Biocompatibility evaluation

Based on the recommended biocompatibility testing addressed in FDA guidance "Use of International Standard ISO-10993", Biological Evaluation of Medical Device part 1: Evaluation and Testing", the following biological effect shall be evaluated:

ISO10993-4 Selection of tests for interactions with blood

ISO10993-5 Tests for in vitro cytotoxicity

ISO10993-7 Ethylene oxide sterilization residuals

ISO10993-10 Tests for irritation and skin sensitization

ISO10993-11 Tests for systemic toxicity(acute systemic toxicity)

USP<85> Bacterial endotoxins teat

4.2. Indication for Use

EpiFaith Syringe is intended for use with an epidural needle for detecting a loss of resistance, which aids a clinician in verifying needle tip placement in the epidural space.

4.3. Packing and Labeling

Packaging: Flat Medical Co., Ltd. will carry out the preparation, packaging and distribution of the test devices.

Labeling: All test devices will must also be labeled "for use in clinical trials only" and be supplied in identical package with the protocol number, randomization number, expiration dates, the name of the sponsor, and information sufficient to identify the trial site and research personnel involved.

4.4. Handling and Storage

The test devices will be handled by the investigator or the designated pharmacist for management and dispensation. All supplies for this study should be kept under adequate security and storage conditions.

5. STUDY CONDUCT

5.1. Visit Schedule

5.1.1. Schedules

The following table details the study schedule of procedures:

Table 2. Schedule of Assessments

Procedures	**Screening(3)**	**Operative period**
	Visit 1	Visit 2
Informed Consent	X	
Inclusion/Exclusion Criteria(1)	X	X
Medical History	X	
Demography	X	
Physical Examination	X	
Randomization		X
Epidural Space Localization Planning		X
Epidural Space Localization with Study Test Device		X
Concomitant Therapy		X
Adverse Events(2)		X

(1): For exclusion criteria #1, platelet count and INR in admission medical record are acceptable.
(2): The AEs and SAEs will be recorded from the start to the end of epidural space localization.
(3): All activities listed for the Screening Visit should be accomplished prior to those listed in the Operative Visit.

5.1.2. Eligibility and inform consent

Subjects will be screened prior to the start of the study treatment. All assessments will be performed after the subjects have signed and dated the inform consent form.

The investigator or a designee will explain the nature of the study to subjects who will undergo surgery requiring epidural space localization. The subject will be given an informed consent form to be read carefully before agreeing to take part in the study and before the study-specific procedures take place. The informed consent form should be reviewed, signed, and dated by the subject and counter-signed by the investigator. A copy of the statement will be given to the subject, and the original should be maintained by the investigator in the site master file. After informed consent being obtained, designed procedures and assessments will be initiated to determine eligibility.

5.1.3. Visit 1 – Screening Visit

After a subject has signed the informed consent document, he or she will be enrolled after screening for selection criteria. The following assessments should be evaluated at this visit:

- Sign informed consent.
- Check subject's eligibility: inclusion and exclusion criteria.
- Collect significant medical history and ASA physical status.
- Collect demographic data.
- Conduct physical exam: At enrollment, it should be also recorded a complete physical exam, height, and weight.

5.1.4. Visit 2 – Operative Visit (End of Treatment/Study)

All activities listed for the Screening Visit should be accomplished prior to those listed in the Operative Visit. The following assessments should be evaluated in operative Visit:

- Check subject's eligibility: exclusion #5 should be excluded. Platelet count, INR, and skin infection at injection site must be re-checked before epidural space localization.
- Randomization and assign randomization number.
- Decide the procedure of epidural space localization.
- Measure all designated outcomes of epidural space localization as following:
  - Success of epidural localization
  - Time to identify the epidural space
  - Duration of the epidural space localization procedure
  - Number of attempts
  - Number of the occurrence of false positive

- The distance from the skin to the epidural space
- Number of change insertion segment

- Record concomitant therapy.
- Record adverse events, if AEs occur.

5.2. Procedures

5.2.1. Informed consent

The subjects must personally sign and date the latest approved version of the informed consent form before any study specific procedures are performed.

Written versions of the subject information and informed consent will be presented to the subjects detailing no less than: the exact nature of the study; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the subject is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

The subject will be allowed as much time as wished to consider the information, and the opportunity to question to decide whether they will participate in the study. Written informed consent will then be obtained by means of subject dated signature and dated signature of the person who presented and obtained the informed consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorized to do so by the principal investigator. A copy of the signed informed consent will be given to the subjects. The original signed form will be retained at the study site.

5.2.2. Eligibility

Eligibility will be evaluated at Visit 1 and Visit 2. Subjects must meet all of the inclusion and none of the exclusion criteria to be considered eligible for the study.

5.2.3. Demographic data and medical history

Demographic data and medical history will be collected.

The significant medical history should be recorded, including chronic diseases, allergic history, and surgical history. The medical history will be tracked back for 3 months prior to surgery. The ASA physical status should be also noted.

5.2.3.1. ASA physical status classification system

The ASA physical status classification system (October 15, 2014) is a system for assessing the fitness of patients before surgery.

Table 3. The ASA Physical Status Classification System

ASA PS Classification	Definition	Examples, including, but not limited to:
ASA I	A normal healthy patient	Healthy, non-smoking, no or minimal alcohol use
ASA II	A patient with mild systemic disease	Mild diseases only without substantive functional limitations. Examples include (but not limited to): current smoker, social alcohol drinker, pregnancy, obesity (30 < BMI < 40), well-controlled DM/HTN, mild lung disease
ASA III	A patient with severe systemic disease	Substantive functional limitations; One or more moderate to severe diseases. Examples include (but not limited to): poorly controlled DM or HTN, COPD, morbid obesity (BMI ≥40), active hepatitis, alcohol dependence or abuse, implanted pacemaker, moderate reduction of ejection fraction, ESRD undergoing regularly scheduled dialysis, premature infant PCA < 60 weeks, history (>3 months) of MI, CVA, TIA, or CAD/stents.
ASA IV	A patient with severe systemic disease that is a constant threat to life	Examples include (but not limited to): recent (< 3 months) MI, CVA, TIA, or CAD/stents, ongoing cardiac ischemia or severe valve dysfunction, severe reduction of ejection fraction, sepsis, DIC, ARD or ESRD not undergoing regularly scheduled dialysis
ASA V	A moribund patient who is not expected to survive without the operation	Examples include (but not limited to): ruptured abdominal/thoracic aneurysm, massive trauma, intracranial bleed with mass effect, ischemic bowel in the face of significant cardiac pathology or multiple organ/system dysfunction
ASA VI	A declared brain-dead patient whose organs are being removed for donor purposes	

The addition of "E" to the ASAPS (e.g., ASA 2E) denotes an emergency surgical procedure. The ASA defines an emergency as existing "when the delay in treatment of the patient would lead to a significant increase in the threat to life or body part."

Abbreviations used: ASA: American Society of Anesthesiologists, DM: diabetes mellitus; HTN: hypertension; COPD: chronic obstructive pulmonary disease; ESRD: end-stage renal disease; PCA: post conceptional age; MI: myocardial infarction; CVA: cerebrovascular accident; TIA: transient ischemic attack; CAD: coronary artery disease; DIC: disseminated intravascular coagulation; ARD: acute respiratory disease.

5.2.4. Physical examination

A complete physical examination will be performed at the screening visit, including the examination of general appearance, skin, cardiovascular, pulmonary, abdomen, neurological system and musculoskeletal/joints. Height and weight will be also collected at Visit 1.

5.2.5. Epidural space localization procedure

Subjects will undergo the surgical procedure using epidural space localization in a medical center with appropriate facilities and by appropriately trained personnel.

Epidural space localization planning will be completed before the epidural space localization. The plan should be recorded, and the records should include surgery name, insertion segment.

During epidural space localization, the subject are in the lateral position. After cleaning and draping the area, a local anesthetic is infiltrated at the insertion site of epidural needle.

Anesthesiologist inserted the epidural needle at least 3cm to pass the subcutaneous tissue. Pull out the stylet and attach the filled EpiFaith syringe. In Group A, the EpiFaith syringe is filled with air; in Group S, the EpiFaith syringe is filled with saline. Then, push the plunger to create a continuous pressure inside the syringe. When the needle arrived the epidural space, due to LOR occurred, the piston of EpiFaith syringe will move forward. The clear visual signal can warn the operator the localization of needle tip. **After the detection of LOR, the catheter will be inserted though the needle. When the catheter can protrude from the needle tip at least 3cm, which can be identified by the graduations on its surface, the test dose (2 ml of 2% lidocaine) of anesthetic will be injected. After injection for 15min, the cold sensation test will be performed, by comparing the perception of cold of alcohol sponges between the blocked dermatomes and face. The tests will be bilaterally, and repeated 3 times in 3 difference dermatomes on each side.**

If the visual signal occurs but the catheter cannot be inserted to protrude the needle tip at least 3 cm, which means the false positive occurs.

If the catheter is inserted successfully and the test dose of anesthetic is injected, but the result of cold sensation test shows the perception of cold exists in the blocked dermatomes by cold sensation test and exclude the reason is due to dose and drug failure, which also means the false positive occurs.

If the inadvertent dural puncture occurs, the success of epidural localization will be recorded failed. There is no necessary to record all secondary outcome. The physician can use the traditional LOR syringe or other method to compete the procedure.

The process of epidural space localization will be simultaneously recorded by video.

5.2.5.1. The duration and attempt of epidural localization

The designated assessments of duration and attempt of epidural space localization are defined as below:

- Success of epidural localization is defined as the catheter can be inserted into epidural space **successfully, no cold perception in the blocked dermatomes after the injection of anesthetic by cold sensation test, and** no occurrence of inadvertent dural puncture.
- The time to identify the epidural space is defined as the time of the successful localization from the syringe attached to the Tuohy needle to the occurrence of LOR signal.
- Duration of the epidural space localization procedure is defined as the time from the first puncture of skin to the successful insertion of the epidural catheter.
- Number of attempts is defined as a new puncture of the skin.
- Number of the occurrence of false positive is defined as the insertion of the epidural catheter is unsuccessful **or the perception of cold exists in the blocked dermatomes after the injection of anesthetic by cold sensation test.**
- The distance from the skin to the epidural space.
- Number of change insertion segment

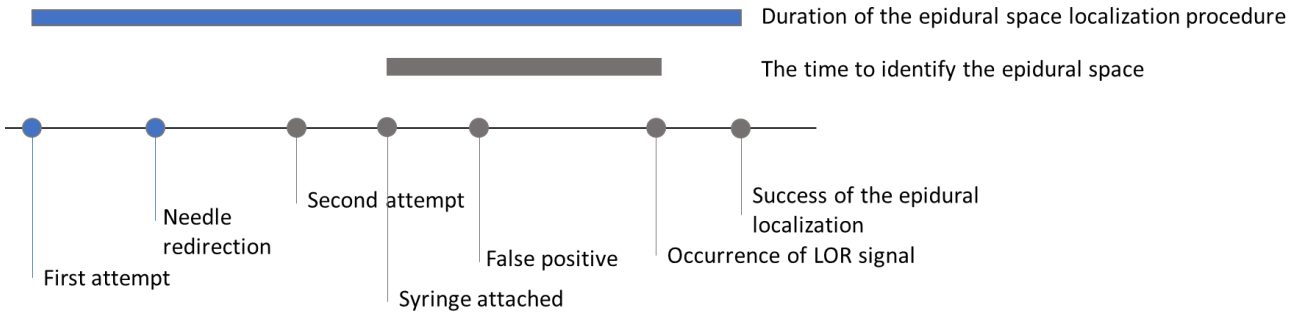

Fig. 6. The definition of the outcome measurement of this study

5.3. Data Management

5.3.1. Data collection

Source documents are original documents, data, and records from which subjects' CRF data are obtained. All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the subject will be referred to by the study screening and randomization number/code, not by name.

Designated investigator staff must enter the information required by the protocol onto the Case Report Forms (CRFs) that are printed on 3-part, non-carbon required paper. Field monitors will review the CRFs for completeness and accuracy, and instruct site personnel to make any required corrections or additions. The CRFs are forwarded to the Medical Documents Reception Center of sponsor or a Contract Research Organization (CRO) by field monitors or by the investigational site, one copy being retained at the investigational site. Once the CRFs are received by sponsor or the CRO, their receipt is recorded, the original copy is placed in Central Files and the non-carbon required copy is forwarded to the responsible medical data management staff for processing. All CRFs sent to sponsor or the CRO by investigational sites are reviewed upon receipt for any serious adverse events.

5.3.2. Data quality assurance

Data items from the CRFs will be entered into the study database. Subsequently, Data Management staff, using error messages printed from validation programs and database listings, will systematically check the information entered into the database. The data manager will correct obvious errors. Other errors or omissions will be sent electronically to the CRA via a Clarification Form to be reconciled with the investigational site. The CRA will obtain the resolution and submit the Clarification Form back to Data Management where the updates will be made to the database. A copy of the Data Clarification Form with the corrected entry will then be printed and sent back to the CRA to obtain the appropriate signatures from the site. The signed Clarification Form will be sent back to Data Management to be filed with the original CRFs. Quality control audits of all key safety and efficacy data in the database will be made after entering data from each visit.

When the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after that time can only be made by joint written agreement between the Clinical Trial Leader, the Trial Statistician and the Data Manager.

If requested, the investigator is to provide to the sponsor, applicable regulatory agencies, and/or applicable ethical review boards, direct access to original source documents. The sponsor or its

representatives will periodically check a sample of the recorded subject data against source documents at the study site.

6. ADVERSE EVENTS

6.1. Adverse Events

6.1.1. Adverse event (AE)

An AE or adverse event is:

Any untoward medical occurrence in a patient or other clinical investigation subject taking part in a trial of a medical device, which does not necessarily have to have a causal relationship with the device under investigation.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the device, whether or not considered related to the device.

6.1.1.1. Adverse device effect (ADE)

All untoward and unintended responses to the medical device.

The phrase "responses to a medical device" means that a causal relationship between the device under investigation and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

All cases judged by either the reporting medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the device qualifies as a device effect.

This also includes any event resulting from insufficiencies or inadequacies in the instruction for use or deployment of the device and includes any event that is a result of a user error.

All AEs will be reported from the start of epidural space localization to the end of epidural space localization.

6.1.2. Serious adverse event (SAE)

- Led to death
- Led to fetal distress, fetal death or congenital abnormality or birth defect.
- Led to serious deterioration in the health of the subject that
  - Resulted in a life-threatening illness or injury

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the subject is at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it are more severe.

- Resulted in a permanent impairment of a body structure or a body function
- Required in-patient hospitalization or prolongation of existing hospitalization
- Resulted in medical or surgical intervention to prevent permanent impairment to a body structure or a body function
- Other important medical events*

*Other events that may not result in death, are not life threatening, or do not require hospitalization, may be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above

To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe", which are not synonymous, the following note of clarification is provided:

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

All SAEs will be reported from the start of epidural space localization to the end of epidural space localization.

6.1.2.1. Serious adverse device effects (SADE)

A serious adverse device effect (SADE) is any untoward medical occurrence seen in a patient that can be attributed wholly or partly to the device which resulted in any of the characteristics or led to a characteristics of a serious adverse event.

SADE is also any event that may have led to these consequences if suitable action had not been taken or intervention had not been made or if circumstances has been less opportune.

All cases judged by either the reporting medically qualified professional or the sponsor.

6.1.2.2. Unanticipated adverse device effect (UADE)

Any serious adverse device effect on health or safety or any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that related to the rights, safety or welfare of the subject.

6.1.3. Severity of adverse events

The grade refers to the severity of the AE using CTCAE Version 4.03 (published on June 14, 2010). The CTCAE displays Grade 1 to 5 with unique clinical descriptions of severity for each AE as shown in below:

Table 4. Grading scales of AEs

Grades of AEs	Description
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care ADL**
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

* Instrumental activities of diary living (ADL) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medication, and not bedridden.

6.1.4. Associated with the use of the test device

An adverse event is considered associated with the use of the device if the attribution is certain, probably/likely, possible, or unlikely by the definitions listed as follows. The causal relationship between AEs and study device refers to WHO-UMC system for standardized case causality assessment.

Table 5. Causality categories between AEs and study device

Causality term	Assessment criteria*
Certain	● Event or laboratory test abnormality, with plausible time relationship to study device use ● Cannot be explained by disease or other medical interventions ● Response to withdrawal plausible (pathologically) ● Event definitive phenomenologically (i.e. an objective and specific medical disorder or a recognized phenomenon) ● Rechallenge satisfactory, if necessary
Probable / Likely	● Event or laboratory test abnormality, with reasonable time relationship to study device use ● Unlikely to be attributed to disease or other medical interventions ● Response to withdrawal clinically reasonable ● Rechallenge not required
Possible	● Event or laboratory test abnormality, with reasonable time relationship to study device use ● Could also be explained by disease or other medical interventions ● Information on withdrawal may be lacking or unclear
Unlikely	● Event or laboratory test abnormality, with a time to study device use that makes a relationship improbable (but not impossible) ● Disease or other medical interventions provide plausible explanations

* All points should be reasonably conformed.

6.1.5. Reporting procedure

6.1.5.1. Adverse event (AE)

All AE's occurring during the study observed by the investigator or reported by the subject, whether or not attributed to the device under investigation will be recorded on the CRF as specified in the protocol. All ADE's will be recorded in the CRF.

The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to device, other suspect drug or device and action taken. Follow-up information should be provided as necessary.

The relationship of AEs to the device will be assessed by a medically qualified investigator or the sponsor/manufacturer and will be followed up until resolution or the event is considered stable.

All ADEs that result in a subject's withdrawal from the study or are present at the end of the study, should be followed up until a satisfactory resolution occurs.

6.1.5.2. Serious adverse reaction

As any SAE occurs, regardless of relationship with the procedure or the device, the investigational staff must inform sponsor or its delegate of their knowledge of the event by email, fax or telephone, and shall provide detailed, written reports as soon as possible.

Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form, which must be signed by a member of the investigational staff. The initial report of a serious adverse event may be made by email, and facsimile (fax). In addition, the SAE may also be forwarded to the TFDA by the sponsor within the appropriate time frame as follows:

If an adverse event results in death or is life-threatening, an SAE should be reported to TFDA within 7 days after becoming aware of the event, and shall provide detailed written documents within 15 days after awareness. If an adverse event results in hospitalization, prolonged hospitalization, disability/incapacity, is a congenital anomaly/birth defect, or requires medical and/or surgical intervention, an SAE should be reported to TFDA within 15 days and provide detailed written document after awareness. Any SAE should be reported promptly according to the reporting procedure of each IRB(s).

6.1.6. Managements of AE

The using of EpiFaith syringe will not change the managements of AEs.

Table 6. The managements of common AEs related the procedure of epidural localization.

AEs	Treatments
Post puncture headache	**Supporting treatment such as rehydration, simple analgesics, opioids and anti-emetics may control the symptoms in milder cases. Generally, >85% of headaches after lumbar puncture will resolve without any specific treatment. Depending on the severity of the headache, prolonged hospital stay for better care and procedure such as blood patch may be required.**
Accidental intravascular catheter placement	**The intravascular catheter can either be withdrawn (1 cm at a time then flushed with saline and aspirated) until no more blood is be aspirated, or it can be totally removed and replaced.**
Accidental subarachnoid catheter placement	**The risk of inadvertently administering an epidural dose intrathecally. The headache may occur, and prolong hospital stay for better care and procedure such as blood patch may be required.**
Bleed at needle entry area	**Clean the puncture area with sterile protocol.**

6.2. Data Safety Monitoring Plan

An Independent safety monitor (anesthesiologist) will call for terminating the study early if more than 5 subjects experience inadvertent dural puncture.

7. STUDY ENDPOINTS

7.1. Primary Endpoint

- Success of epidural localization

  (defined as **the catheter can be inserted into epidural space successfully, no cold perception in the blocked dermatomes after the injection of anesthetic by cold sensation test, and no occurrence of inadvertent dural puncture.**)

7.2. Secondary Endpoint

(1) The time to identify the epidural space (defined as the time of the successful localization from the first syringe attached to the Tuohy needle to the occurrence of LOR signal)

(2) Duration of the epidural space localization procedure

(defined as the time from the puncture of skin to the successful insertion of the epidural catheter)

(3) Number of attempts

(defined as a new puncture of the skin)

(4) Number of the occurrence of false positive

(defined as **the insertion of the epidural catheter is unsuccessful or the perception of cold exists in the blocked dermatomes after the injection of anesthetic by cold sensation test**)

(5) The distance from the skin to the epidural space

(6) Number of change insertion segment

8. STATISTICAL METHODS

8.1. Planned Sample Size

Considering the recommendation given by Lancaster, Dodd &Williamson. A total of 60 subjects (30 subjects per group) will be required in this study to obtain parameters such as ratio, mean and standard deviation which will be used in a sample size calculation for the full-scale trial, and to estimate the rate of participants who drop out of the trial.

8.2. Analysis Population

Intent-to-Treat (ITT) Population: The ITT will consist of all participants who are randomly assigned

to receive study device and have received any study device, irrespective of their protocol adherence. All analyses using the ITT will group participants according to randomized treatment. The ITT will be used as the efficacy analysis set.

Safety Set: The safety set will consist of all participants who received any study device. All analyses using the safety set will group participants according to treatment actually received.

8.3. Demographics and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized by descriptive statistics for two treatment groups. For continuous variables, the number, mean, standard deviation, median, minimum, and maximum values will be presented. A two sample independent t-test will be performed for continuous variables. For categorical variables, the numbers and percentages of subjects in each class will be listed, and the Fisher's exact test for testing two treatment group comparison.

8.4. Efficacy Assessment

Statistical analyses will be reported using summary tables, graphs, and data listings. Analysis are performed with SPSS, Version 20.0 (IBM Corporation, Armonk, NY, USA). The analysis population will be summarized by A and S groups. For categorical variables, frequencies and percentages will be summarized; continuous data will be shown as descriptive statistics. The variables within a normal distribution will be compared using Student's t-tests, and those without a normal distribution will be compared using the Mann-Whitney U test. The number of patients will be compared between the groups using the Fisher's exact test. All information will be summarized and presented in statistical analysis tables. As for data of efficacy and safety variables, no imputation method is applied.

8.4.1. Analysis of primary endpoint

The primary endpoint is the success of epidural localization. The primary analysis will be conducted by Fisher's exact test.

8.4.2. Analysis of secondary endpoints

Student's t-test or Mann-Whitney U-test will be applied to test the comparison between A and S Groups for the time to identify the epidural space, duration of the epidural space localization procedure, the distance from the skin to the epidural space, and the distance from the needle tip to dura.

Number of attempts, number of the occurrence of false positive, and number of change insertion segment will be compared between A and S groups using Fisher's exact test.

8.5. Safety Assessment

Incidence of the adverse events will be summarized. In the case of CTCAE grade summaries, the most severe event will be presented in summary tables in the case of multiple occurrences per patient. The frequency and the percentage of each category will be presented. All safety parameters, including adverse events, adverse device effect, serious adverse event, serious adverse device effects and unanticipated adverse device effect will be listed by A and S groups. The Medical Dictionary for Regulatory Activities (MedDRA) adverse event dictionary will be used to map verbatim adverse events to preferred terms and system organ class. Fisher's exact test will be applied for comparing the incidences of adverse events between treatment groups.

9. ETHICAL AND LEGAL ASPECTS

9.1. Good Clinical Practice

This study must be carried out in compliance with the protocol and in accordance with sponsor/CRO standard operating procedures. These are designed to ensure adherence to Good Clinical Practice, as described in the following documents:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 2016.
2. Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996, Edinburgh, 2000, Washington 2002, Tokyo 2004, Seoul 2008, Fortaleza 2013).

The investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

9.2. Delegation of Investigator Responsibilities

Responsibilities of the investigators conducting the study in addition to those stated before are enumerated below:

- Obtain Institutional Review Board (IRB) approval to conduct the clinical study.
- Provide sponsor with written documentation that the study protocol, any protocol amendments, and the informed consent form have received IRB approval.
- Provide sponsor with a list of IRB members, including their affiliations and qualifications. As an alternative, a General Assurance number (as assigned by the Department of Health and Human Services) fulfills this requirement.

- Report to the IRB as required. The IRB must assume continued responsibility for the study and review the research on an annual basis.
- Maintain a file of all communications with the IRB on issues related to the clinical trial.
- Conduct the study according to the protocol, ICH - GCP guidelines and in accordance with the Declaration of Helsinki.

9.3. Subject Information and Informed Consent

Written informed consent must be obtained from all subjects prior to study participation. The informed consent form documents the information the investigator provides to the subject and the subject's agreement to participate. The investigator will fully explain the nature of the study, along with the aims, methods, anticipated benefits, potential hazards, and discomfort that participation might entail. The informed consent must be signed and dated by each subject or legal representative before entering the study and prior to the performance of any study specific procedures.

Investigational site must provide the sponsor (or designee) with a copy of the informed consent approved by that site's Institutional Review Board (IRB), or Ethics Committee (EC). The subject or the subject's legally authorized representative must sign the informed consent form. The original signed consent form will be retained in the subject's study records, and a copy will be provided to the subject. The sponsor will assure that each informed consent meets the basic elements of informed consent.

9.4. Subject Rights and Confidentiality

9.4.1. Subject confidentiality

The trial staff will ensure that the subjects' anonymity is maintained. The subjects will be identified only by initials and a subjects ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by trial staff and authorized personnel. The study will comply with the Data Protection Act 1998 which requires data to be anonymized as soon as it is practical to do so.

9.4.2. Study discontinuation

The study may be discontinued at any time by the IRB, the TFDA, or other government agencies as part of their duties to ensure that research subjects are protected.

9.5. Protocol Amendments

The investigator is responsible for properly notifying the sponsor of protocol changes or revisions. The investigators without prior written authorization from the sponsor may make no changes to this protocol.

9.6. Approval of the Study Protocol and Amendments

Before the start of the study, the study protocol, informed consent document, and any other appropriate documents will be submitted to the independent ethics committee (IEC)/institutional review board (IRB) with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities, in accordance with local legal requirements.

Test device can only be supplied to the investigator after the sponsor has received documentation on all ethical and legal requirements for starting the study. This documentation must also include a list of the members of the IEC/IRB and their occupations and qualifications. If the IEC/IRB will not disclose the names of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. The IRB General Assurance Number may be accepted as a substitute for this list. Formal approval by the IEC/IRB should preferably mention the study title, study code, study site (or region or area of jurisdiction, as applicable), and any other documents reviewed. It must mention the date on which the decision is made and must be officially signed by a committee member.

Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

The IEC/IRB and, if applicable, the authorities must be informed of all subsequent protocol amendments, in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the informed consent document should also be revised.

The investigator must keep a record of all communication with the IEC/IRB and, if applicable, between a coordinating investigator and the IEC/IRB. This also applies to any communication between the investigator (or the coordinating investigator, if applicable) and the authorities.

9.7. Payment to Subjects/Families

There will be no costs to subjects for any research related activities. All research-related costs will be paid by sponsor- Flat Medical Co., Ltd.(醫盟科技). If subjects do not finish the study, they will not be paid.

9.8. Publication policy

The results from this clinical trial will be published in the journal of Anesthesia & Analgesia.

10. REFERENCES

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