Evaluation the Non-Inferiority of Airmod to Capnostream™35 on Respiratory Rate Monitoring and User Experience Clinical Evaluation

Protocol Number: HF-AM-01-2021

Principal Investigator: <Principal investigator>

Sponsor: Heroic Faith Medical Science Co., Ltd.

Version Number: 3.0

1 October 2021

Identifiers: NCT05263791

Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
1/2/3/4/5/6/8/9/10	Minor fixed of description (no effect with study design) and added supplementary section (10.2).	Found some description errors (no effect with study design). Meanwhile, give further information to complement the protocol.

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STATEMENT OF COMPLIANCE

This study will be conducted in accordance with standard operating procedures of the Sponsor (or designee), which are designed to ensure adherence to Good Clinical Practice (GCP) guidelines as required by the following:

- Principles of the World Medical Association (WMA) Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects (October 2013)
- ICH E6 (R2) Good Clinical Practice: Integrated Addendum to ICH E6 (R1): Guidance for Industry - E6(R2) Good Clinical Practice: Consolidated Guidance, United States (US) Department of Health and Human Services, Food and Drug Administration (FDA) (March 2018)
- ISO 14155: Clinical investigation of medical devices for human subjects - Good clinical practice (July 2020)
- Law of Taiwan Ministry of Health and Welfare regarding clinical studies, including Medical Care Act, Pharmaceutical Affairs Act, Medical Devices Act, Human Subjects Research Act, Regulations on Human Trials and Regulations for Good Clinical Practice
- Title 21 of the US Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and Institutional Review Boards regulations, Part 54 concerning financial disclosure by clinical investigators, Part 58 and 820 concerning Good Laboratory Practice (GLP) for nonclinical laboratory studies and quality system and applicable sections of US 21 CFR Part 812 and/or Part 312

The protocol, informed consent form(s) (ICFs), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB)/Ethics Committee (EC) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: Evaluation the Non-Inferiority of Airmod to Capnostream™35 on Respiratory Rate Monitoring and User Experience Clinical Evaluation

Study Description: This is a prospective, multi-center, pivotal study. The purpose of this study is to evaluate the non-inferiority of Airmod to Capnostream™35 for respiratory rate monitoring and user experience clinical evaluation.

Objectives: The objective of this study is to demonstrate that the performance and safety of Airmod in monitoring respiratory rate is non-inferior to Capnostream™35.

Primary Objective:
To evaluate accuracy and performance of respiratory rate (RR) measurement from Airmod compared to Capnostream™35. The primary objective is to establish the non-inferiority.

Secondary Objectives:

1. To assess the accuracy of respiratory rate measurement by Airmod in comparison with manual-scored auscultation sound during the less sensitive period of Capnography on Capnostream™35.
2. To measure the agreement between AirRR and ManCRR.
3. To evaluate the response time of the first breath detection followed by administration of jaw thrust during the apnea period. The 3rd secondary objective is to compare the response time of Airmod versus Capnography.
4. To compare the influence of subjects to variated breath rates on respiratory rate monitoring in bpm as measured by Airmod, manual-scored and Capnostream™35.
5. To evaluate the safety and usability of Airmod.

Manual-scored Capnography (ManCRR) originated from Capnostream™35 (K150272, Medtronic)
Machine-scored Capnography (CapRR) generated from Capnostream™35 (K150272, Medtronic)
Manual-scored auscultation sound (ManARR) originated from AS-101
Airmod-scored auscultation sound (AirRR) generated from AS-101

Endpoints:

Primary Endpoint:
The difference between AirRR and ManCRR, which is greater than -3 under to establishes non-inferiority. The unit in this calculation is bpm and sampling rate is 1 Hz.

Secondary Endpoints:

1. The accuracy of inhalation classification in the segmentation basis is greater than 82.5% at the 95% CI. The performance metrics (F1-

socre, MAPE) at event level will be demonstrated and target for F1-score > 0.8, MAPE < 0.5.

2. To measure the agreement of AirRR and ManCRR on concordance correlation coefficient, and on their mean and bias by Bland-Altman analysis.
3. Use paired t-test to compare the response time of Airmod versus Capnography on Capnostream™35 after administration of jaw thrust. In the target of $p<0.05$ indicates significance.

4.1. The difference of ManCRR minus AirRR and ManCRR minus CapRR indicates non-inferiority at margin of 3 bpm (M1) and sampling rate 1Hz.

4.2. The difference of ManCRR minus AirRR and ManCRR minus CapRR indicates non-inferiority at margin of 2 bpm (M2) and sampling rate 1Hz.

5. The absence of unanticipated serious adverse device effect (USADE) during study period and the questionnaire.

[Time Frame:
Non-Anesthesia Stage: Up to 40 patients will be randomly assigned to non-anesthesia stage assessment, the measurement will be evaluated after enrollment with ICF, at the non-operating room (NOR) area. (5~30 minutes)
Procedure Stage: From firstly anesthetic administration to end of procedure. (Depends on procedure 10mins ~ few hours)
Non-operating room area (NORA) stage : From transportation of subjects to PACU to discharge from PACU (PAR or PADSS score ≥ 9) (At least 15 minutes)]
The information of patient monitoring period refers to 10.2.1.

Study Population:

By referencing predicate device clinical trials on respiratory rate monitoring in the hospital setting, most of the cases recruited 120+ patients. Considering a 40% withdrawal/dropout rate, we proposed a total enrollment of 300 subjects at the operation room (OR) and NOR area in the hospital. Further information refers to 10.2.2.

Inclusion Criteria:

1. Provision of signed and dated informed consent form.
2. Stated willingness to comply with all study procedures and availability for the duration of the study.
3. Male or female with at least 20 years of age.
4. Fit for intravenous general anesthesia (IVG) as assessed by pre-anesthesia evaluation.

Details of 3 & 4 refer to 10.2.3.

Exclusion Criteria:

1. Presence of neck pain or injuries.
2. Under the use of high-flow nasal cannula ventilation. Other examples refer to 10.2.4.
3. Unable to wear Airmod and Capnostream™35 device related accessories at the investigator's discretion.

4. As a vulnerable population, including legal incapacity or evidence that a subject cannot understand the purpose and risks of the study, regardless of authorized representative support.
5. Unwilling or unable to comply fully with study procedures (including non-toleration of the capnography cannula) due to any disease condition which can raise doubt about compliance and influencing the study outcome.
6. The patient who can't receive operation under IVG anesthesia that suggest by the evaluation of preoperative assessment.

Phase:	Pivotal
Description of Sites/Facilities Enrolling Participants:	This study is intended to conduct in 3 sites in Taiwan, with an equal number of patients will be expected to enroll in all sites but competitive.
Description of Study Intervention:	The investigational product (IP), 'Airmod', is intended to provide professionally trained health professionals with continuous non-invasive measurement and monitoring of respiratory rate in adult patients. It is designed to detect inhalation acoustics and provides respiratory rates based on the analysis of the acoustic signals of breathing sounds collected by the electronic stethoscope. The device is intended for use in hospitals, hospital-type facilities, during intra-hospital transport, and out-of-hospital emergency medical service (EMS) applications that include ground and air transport. The intended for use is further described in 10.2.5.
Study Duration:	Estimated 12 months
Participant Duration:	Approximate 1.5 months for each individual subject to complete all participant visits.

1.2 SCHEMA

Study Flow diagram

Screening
Visit 1, Day -28 ~ -1

Total 300: Obtain informed consent.
Screen potential participants by inclusion and exclusion criteria.
Obtain medical history and demographic data.
Perform physical examination and vital signs.
Refer to Section 1.3, Schedule of Activities

Treatment Visit 2, Day 1 + 14	Administer study intervention. Refer to Section 1.3, Schedule of Activities

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	**Screening** [a]	**Treatment** [a]
Visit Number	1	2
Visit Days	-28 ~ 1	1
Allowed visit window (days)		+14
Informed consent	X	
Criteria evaluation	X	
Medical history	X	
Demographic data [b]	X	
Physical examination [c]	X	
Vital signs [d]	X	
Study intervention administration		X [e]
PAR assessment [f]		X [g]
PADSS assessment [f]		X [g]
Adverse event review and evaluation		X

a. Screening and treatment can be the same day.
b. Demographic data include date of birth and gender.
c. Physical examination includes general appearance, weight and height, HEENT (head, eyes, ears, nose, and throat), mouth, skin, neck (including thyroid), lymph nodes, spine, cardiovascular system, respiratory system, gastro-intestinal system, nervous system, musculoskeletal system, blood and blood forming organs, mental status, and other body systems if applicable.
d. Vital signs include body temperature, sitting blood pressure and pulse rate.
e. The administered anesthetic medication and dosage, surgery type, start and stop time of surgery will also be collected.
f. Post Anesthetic Recovery (PAR) and Post Anesthetic Discharge Scoring System (PADSS) will be assessed upon admission and every 15 minutes after transferring to post anesthesia care unit (PACU).
g. Subject will be discharged when PAR or PADSS score ≥ 9, consider as complete the study.

2 INTRODUCTION

2.1 STUDY RATIONALE

Longitudinal general population-level estimates of sedative medication use are lacking. There are a few studies that show the use of sedative medications has substantially risen among various countries across the population [1-3], which gender and age disparities with respect to sedative use [1, 4-6].

Sedation is widely used in the reduction of irritability or agitation, which could be performed in OR or NOR, by relieving anxiety, reducing pain, and providing amnesia, sedation techniques have the potential to render potentially uncomfortable diagnostic and therapeutic procedures more comfortable and acceptable for patients [7]. Sedation for medical procedures is provided in a variety of clinical settings by medical personnel with differing levels of education and training, although generally a safe practice, there is a degree of risk associated with sedation practice [8]. This is because sedation is a continuum and it is not possible to predict how an individual patient will respond. At a certain level of sedation, the natural drive to breathe can be inhibited, therefore an adequate ventilation of the patient is important [7, 8]. These risks have been recognized but the incidence of significant morbidity or mortality is difficult to ascertain.

One of the key components of managing sedation is knowing how to manage the patient's airway, while monitoring using capnography is the most reliable method, making sure that patients are properly ventilating [9, 10]. Adverse events could be preventable with the adequate monitoring.

Respiratory rate (RR) is among the first vital signs to reflect the change in patient's condition and is usually assessed clinically, by counting chest wall movements. This is time consuming, may be difficult to perform in busy post-anesthesia care units, and is limited by its intermittent nature. Monitoring RR using continuous end-tidal carbon dioxide ($EtCO_2$), by capnography for the early detection of respiratory changes during the sedation is then highly useful [8, 11].

There is an urgent need for a robust, low-cost method that can help frontline healthcare workers to measure RR quickly. An effective way for improving efficiency of rate estimations is incremental and continuous analysis of time intervals instead of counting events in a fixed time interval, thus, using deep learning to assist with such tasks.

The purpose of this study is to compare the respiratory rate assessment in adult patients at hospital, on the deep learning-enable RR monitor software, Airmod, to the commercial respiratory monitor, Capnostream™35, to indicate non-inferiority.

2.2 BACKGROUND

Sedation is commonly prescribed to reduce the patient's anxiety, discomfort and pain during certain procedures. All sedatives suppress the central nervous system in a dose-dependent manner, usually accompanied by a reduction in CO_2 responsiveness in the medullary respiratory center. One of the most common adverse effect associated with sedation is respiratory depression, and the greater the degree of sedation, the greater the degree of respiratory depression observed [12].

Monitoring of sedation is of great importance, not only avoid inadequate or over sedation, also assuring quality care and minimizing risk of adverse events [8, 13]. Given that capnography is the most reliable method to confirm airway device placement and monitor ventilation, as the current gold standard method [9, 14]. After initial placement, loss of the waveform can indicate movement of the tube, possible esophageal placement or circuit disconnection, which provides a continuous assurance of functional tube placement. In a 2001 study of 345 intubations, capnography had a sensitivity and specificity of 100% for correct placement [15].

The capnography waveform represents air movement in the lungs, starts at the beginning of exhalation, and senses air from dead space in the upper airway and bronchi. As carbon dioxide (CO_2) is a product of metabolism transported via perfusion and expelled through ventilation, the End-tidal carbon dioxide ($EtCO_2$) waveform adds an objective measurement on counting the respiratory rate (RR), where it increases as CO_2 rises, and decreases as CO_2 falls [16]. This provided real-time feedback on the patient's conditions, indicating the response to a treatment, where plans can be quickly adjusted when capnography is used to monitor trends.

The importance of monitoring respiratory rate as a key vital sign has been well defined in medicine [17]. An abrupt alteration in respiratory rate can help detect changes in the status of a patient during a crucial period where modifications in management might be needed. Respiratory monitoring is important for both patients receiving general anesthesia as well as for those who require sedation [17].

Capnostream™35 is a commercially available device (cleared by FDA, MHLW/PMDA, TFDA and CE-Marked), a portable respiratory monitor that offers comprehensive respiratory monitoring which helps medical expert to respond earlier and intervene sooner if the patient is showing signs of respiratory compromise. The monitor provides information to help support clinical decisions and may improve workflow [18].

Airmod is a software application designed to aid healthcare professionals by monitoring a patient's breathing in real time. It can detect inhalation acoustics and provides respiratory rates based on the analysis of the acoustic signals of breathing sounds collected by the electronic stethoscope. The noise-cancelling technology in the Airmod helps to reduce ambient noises and acoustic feedback. The AS-101, a digital stethoscope, performs sound processing, with the bandwidth covering the frequency range of 20-2000Hz. Auscultation sound is then transferred to the headphone or the mobile device speaker allowing the user to switch among four channels to listen to and view the spectrogram coming from different auscultation locations.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To evaluate accuracy and performance of respiratory rate (RR) measurement from Airmod compared to Capnostream™35. The primary objective is to establish the non-inferiority.	The difference between AirRR and ManCRR, which is greater than -3 under establishes non-inferiority. The unit in this calculation is bpm and sampling rate is 1 Hz. [Time Frame: Non-Anesthesia Stage: Up to 40 patients will be randomly assigned to non-anesthesia stage assessment, the measurement will be evaluated after enrollment with ICF, at the NOR area. (5~30 minutes) Procedure Stage: From firstly anesthetic administration to end of procedure. (Depends on procedure 10mins ~ few hours) NORA stage : From transportation of subjects to PACU to discharge from PACU (PAR or PADSS score ≥ 9) (At least 15 minutes)] The information of patient monitoring period refers to 10.2.1.	
Secondary		
To assess the accuracy of respiratory rate measurement by Airmod in comparison with manual-scored auscultation sound during the less sensitive period of Capnography on Capnostream™35.	The accuracy of inhalation classification in the segmentation basis is greater than 82.5% at the 95% CI. The performance metrics (F1-socre, MAPE) at event level will be demonstrated and target for F1-score > 0.8, MAPE < 0.5.	The principal investigator and research members will determine the less sensitive period. To assess the precision and recall rate of Airmod deep learning algorithm, the F1-score build up and bind the hierarchy positive and negative metrics all together. It is generally described the harmonic mean of the two. Besides, the MAPE enhanced the difference power of error prediction by keep positive and negative errors from cancelling out each other. The relative errors are independent with the scale of target.
To measure the agreement between AirRR and ManCRR.	To measure the agreement of AirRR and ManCRR on concordance correlation	Bland-Altman analysis is used to measure the consistency of continuous data from two

	coefficient, and on their mean and bias by Bland-Altman analysis. [Time Frame: Non-Anesthesia Stage: Up to 40 patients will be randomly assigned to non-anesthesia stage assessment, the measurement will be evaluated after enrollment with ICF, at the NOR area. (5~30 minutes) Procedure Stage: From firstly anesthetic administration to end of procedure. (Depends on procedure 10mins ~ few hours) NORA stage : From transportation of subjects to PACU to discharge from PACU (PAR or PADSS score ≥ 9) (At least 15 minutes)] The information of patient monitoring period refers to 10.2.1.	distinct measurements. Therefore, the likelihood of AirRR and ManCRR will be quantified and visualized on the assumption of fixed observer and pairs Bland-Altman analysis. Further information refers to 10.2.6.
To evaluate the response time of the first breath detection followed by administration of jaw thrust during the apnea period. The 3rd secondary objective is to compare the response time of Airmod versus Capnography.	Use paired t-test to compare the response time of Airmod versus Capnography on Capnostream™35 after administration of jaw thrust. In the target of $p<0.05$ indicates significance.	The principal investigator and research members will determine the apnea period and the first effective breath.
To compare the influence of subjects to variated breath rates on respiratory rate monitoring in bpm as measured by Airmod, manual-scored and Capnostream™35.	1. The difference of ManCRR minus AirRR and ManCRR minus CapRR indicates non-inferiority at margin of 3 bpm (M1) and sampling rate 1Hz. 2. The difference of ManCRR minus AirRR and ManCRR minus CapRR indicates non-inferiority at margin of 2 bpm (M2) and sampling rate 1Hz. [Time Frame: Non-Anesthesia Stage: Up to 40 patients will be randomly assigned to non-anesthesia stage assessment, the measurement will be evaluated after enrollment with ICF, at the NOR area. (5~30 minutes) Procedure Stage: From firstly anesthetic administration to end of procedure. (Depends on procedure 10mins ~ few hours)	Capnography is inherently limited in certain circumstances which may cause ineffectively detecting CO_2, including movement, nasal cannula drop, blocked, or other situations. Airmod is superior to capnography in these limitations since it detects and measure breath sound directly. 1. The difference between ManCRR and AirRR is comparing with the difference between CapRR and ManCRR to indicate the bias of Airmod are non-inferior to the reference devices at the

	NORA stage : From transportation of subjects to PACU to discharge from PACU (PAR or PADSS score ≥ 9) (At least 15 minutes)] The information of patient monitoring period refers to 10.2.1.	margin of 3 bpm, which also demonstrates substantial equivalence. 2. To evaluate whether Airmod can approach a strict standard suggested by clinicians, the difference between ManCRR and AirRR is comparing with the difference between CapRR and ManCRR to indicate the bias of Airmod are non-inferior to the reference devices at the margin of 2 bpm, which indicates the largest clinically acceptable difference. Part of the measurement result within subject will be censored and excluded in the paired non-inferiority test. The principle of exclusion is based on the failure event/period of Airmod or CapnostreamTM35 reported by investigator. The report will be confirmed by the principal investigator, the data prior to discontinuation and after machine failure being fixed is still included. Examples of excluded measurement refer to 10.2.7.
To evaluate the safety and usability of Airmod.	The absence of unanticipated serious adverse device effect (USADE) during study period and the questionnaire.	

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a prospective, multi-center, pivotal study. The purpose of this study is to evaluate the non-inferiority of Airmod to Capnostream™35 for respiratory rate monitoring. Subgroup analyses will be performed, details are described in statistical analysis plan (SAP).In the total of 300 subjects enrolled at the OR and NOR area in the hospital, the interim analysis will be performed at the enrollment of 150 subjects during study period. (using OBrien-Fleming to determine α=0.00153)

Safety will be assessed by the investigator(s) and will be monitored until the end of the study. All Adverse Event(s) (AE) and Serious Adverse Event(s) (SAE) occurring during the study period will be followed until the event is considered stable or until full resolution.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

A new simple tool to monitor patient's respiratory rate is needed which benefits both patients and medical experts. The current standard for RR measurement is capnography ($EtCO_2$). Capnostream™35, a commercially available device that provides functions that are required for the standard of care along with benefits that are conducive to the study (capnography, sufficient battery life, suitable in size and portable), is selected as the study control device. So, in order to establish whether Airmod is no worse than the commercially available device for which the performance of RR monitoring has been determined, the clinical study was planned.

4.3 JUSTIFICATION FOR DOSE

Not applicable in this study.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3. The end of the study is defined as the time point when the subject discharged from post anesthesia care unit (Post Anesthetic Recovery [PAR] or Post Anesthetic Discharge Scoring System [PADSS] score ≥ 9; these are assessed by the site staff upon admission and every 15 minutes after the subject transfer to PACU), or the end of non-anesthesia period determined by principal investigator.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

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

1. Provision of signed and dated informed consent form.
2. Stated willingness to comply with all study procedures and availability for the duration of the study.
3. Male or female with at least 20 years of age.
4. Fit for intravenous general anesthesia (IVG) as assessed by pre-anesthesia evaluation.

Details of 3 & 4 refer to 10.2.3.

5.2 EXCLUSION CRITERIA

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

1. Presence of neck pain or injuries.
2. Under the use of high-flow nasal cannula ventilation. Other examples refer to 10.2.4.
3. Unable to wear Airmod and Capnostream™35 device related accessories at the investigator's discretion.
4. As a vulnerable population, including legal incapacity or evidence that a subject cannot understand the purpose and risks of the study, regardless of authorized representative support.
5. Unwilling or unable to comply fully with study procedures (including non-toleration of the capnography cannula) due to any disease condition which can raise doubt about compliance and influencing the study outcome.
6. The patient who can't receive operation under IVG anesthesia that suggest by the evaluation of preoperative assessment.

5.3 LIFESTYLE CONSIDERATIONS

Not applicable in this study.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

The recruitment of subjects will be conducted according to GCP and local regulations. Subjects will be recruited through appropriate measures, including but not limited to posters established for the specific purpose of recruiting. There will be a reimbursement for the participant at the time on signing informed consent form in order to keep the retention.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

The investigational product (IP), 'Airmod', manufactured by Heroic Faith Medical Science Co., Ltd., is intended to provide professionally trained health professionals with continuous non-invasive measurement and monitoring of respiratory rate in adult patients. It is designed to detect inhalation acoustics and provides respiratory rates based on the analysis of the acoustic signals of breathing sounds collected by the electronic stethoscope. The device is intended for use in hospitals, hospital-type facilities, during intra-hospital transport, and out-of-hospital emergency medical service (EMS) applications that include ground and air transport. The intended for use is further described in 10.2.5.

In this study, Airmod will be used along with AS-101 (AccurSound Electronic Stethoscope, a commercially available device in Taiwan). There are no known contraindications and are not designed for use in patients unable to be assessment by stethoscope such as who require the use of high-flow nasal cannula.

Table 1 and 2 provides a list of devices and accessories components that may be used in the study.

Table 1. Airmod and Accessory Components

Product	Model or Version or Material
Airmod Software	Airmod V1
Additional Accessories	Devices with operating system standard Android 10/11, RAM 8G, 128G; chipset processing power equivalent or superior to Snapdragon™ 855.
	AccurSound Electronic Stethoscope model AS-101 (herein referred to 'AS-101')
	Surgical tape

Table 2. Capnostream™35 Devices and Accessory Components

Product	Model or Version or Material
Hardware (monitor)	Capnostream™35 Portable Respiratory Monitor PM35MN
Capnostream™35 Software	Monitor: 01.00.06.05 CO_2: 01.14
Unit dimensions	(Height) 213 mm × (Width) 137 mm × (Depth) 55 mm
Power supply	Input Voltage 100-240 V, 50/60 Hz, ± 10%
Waveform sampling rate	20 samples/sec
Additional Accessories	'Medtronic' Microstream™ etCO2 Sampling Lines (Smart CapnoLine Plus O_2, herein referred to 'sampling lines')

6.1.2 DOSING AND ADMINISTRATION

Subjects will be monitored with the devices Airmod and Capnostream™35 simultaneously on Visit 2; both devices should be ready and apply correctly on the subject before sedation.

- Airmod administration procedure

  Preparation

  1. The device with Airmod should have enough battery life that last for the whole study process. Attach the device with Airmod with the AS-101 using type- C to type-C cable.
  2. Place the auscultation sensor on the patient neck (left or right-side plain area of thyroid cartilage), secure with surgical tape.
  3. Click on the 'Airmod' on the screen of the device to enter the software interface. When the device with Airmod and AS-101 are properly connected, an indicator light should come up, and then are able to click on the start/stop button to start monitoring.
  4. By clicking the start/stop button, immediately breathing sound and spectrogram should be presented via speaker and display screen respectively, and if the signal or reception is unstable, adjust the auscultation sensor or secure with surgical tape to improve.

  Monitoring (start time)

  5. To start recording the monitoring for the study, on the display screen, select start/ stop button and entering the patient ID.

  Monitoring (end time)

  6. To end monitoring and terminate the saving process, on the display screen, select the start/stop button. This procedure should be done at the time point where the subject is ready to discharge from post anesthesia care unit (PACU) or the end of non-anesthesia period, which compliance with the criteria PAR or PADSS score ≥ 9 or determined termination by principal investigator.

- Capnostream™35 administration procedure

  Preparation

  1. Capnostream™35 should have enough battery life that last for the whole study process.
  2. To set up for the subject, on the monitoring display screen, select menu -> action -> patient admin -> insert the subject number.
  3. Connect the sampling line to the monitor, rotate it clockwise until it can no longer be turned; and also connect the sampling line to the subject nostril, adjust the tightness at the lower band to fit on the subject. When properly connected, the monitor will immediately begin to search breaths, then present $EtCO_2$ value and waveform on the display screen after 3.4 ~ 5.0 second.
  4. Connect the pulse oximetry line to the monitor and clip the pulse oximetry probe onto the finger of subject. When properly connected, the monitor will present SPO_2 value on the display screen after 3.4 ~ 5.0 second.
  5. To start storing the report and output to SD card, on the monitoring display screen, select menu -> report -> store report -> real-time full continuous transfer -> choose to save in SD card or USB drive -> save report.

  Monitoring (start time)

  6. The monitoring period starts once the last step (save report) has been done.

Monitoring (end time)

7. To end monitoring and terminate the saving process, on the monitoring display screen, select menu -> report -> store report -> active report -> stop. This procedure should be done at the time point where the patient is ready to discharge from PACU or the end of non-anesthesia period, which compliance with the criteria PAR or PADSS score ≥ 9 or determined termination by principal investigator.

The administered anesthetic medication and dosage, surgery type, start and stop time of surgery will be collected during surgery.

The medical records of subjects will be confirmed on allowed visit window (within 14 days).

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

The investigator and study staff will be responsible for the accountability of all clinical supplies (dispensing, inventory, and record keeping) following the Sponsor's instructions. In this matter, the investigator and study staff must adhere to GCP guidelines, as well as national requirements. Under no circumstances will the investigator allow the investigational product to be used other than as directed by this protocol. Clinical supplies will be dispensed only by an appropriately qualified person and will not be dispensed to any individual who is not enrolled in the study. An accurate and timely record of the receipt of all clinical supplies and dispensing of investigational product to the subject must be maintained.

The supplies and inventory records must be made available, on request, for inspection by the Sponsor (or its designee) or a representative of a regulatory authority. All unused investigational product is to be returned to the Sponsor at the conclusion of the study, unless provision is made by the Sponsor for destruction of supplies at the study site. On completion of investigational product accountability and reconciliation procedures by study site personnel and documentation procedures by Sponsor personnel, investigational product that is to be returned to the Sponsor, if necessary, must be boxed and sealed and shipped back to the Sponsor following all local regulatory requirements.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

The investigational materials will be obtained and/or packaged and labeled in a manner consistent with the study design including but not limited to product name, model number, lot number, quantity, shelf life, manufacturing date, company name, company address, manufacturer name and manufacturer address.

Labels will be non-removable in nature. Sample labels for the primary package containing the investigational products are including but not limited to product name, model number, material, lot number, quantity, shelf life, manufacturing date, company name, company address, manufacturer name, manufacturer address, study number and storage condition.

6.2.3 PRODUCT STORAGE AND STABILITY

The investigational product will be stored in accordance with labelled storage conditions. The investigation products (IPs) must be kept strictly separate and in a different location than non-study

commercially available product. The IP should be kept at 0°C to 40°C (32°F to 104°F) and humidity level 15% to 90% until time of use. No damage should appear on the packaging and/or device before using.

Temperature monitoring is required at the storage location to ensure that the investigational product is maintained within an established temperature range. The investigator is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

6.2.4 PREPARATION

Set up for the device with Airmod and Capnostream™35 is required, manual book and a quick guild card along with the product information will be provided for the user included in the study training materials. The device data transfer process will be tested and verified during the site initiation process.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

This study will not be randomized and blinded.

6.4 STUDY INTERVENTION COMPLIANCE

Records of treatment administration for each subject will be kept during the study.

6.5 CONCOMITANT THERAPY

Not applicable in this study.

6.5.1 RESCUE MEDICINE

Not applicable in this study.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

If subject discontinued without administered study intervention, no further evaluations are needed.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Participant unable to receive Airmod and/or Capnostream™35 and their device related accessories.
- After adjustment, noises (such as those caused by air leak continue to pronounce-affect signal quality) continue to be pronounced, and cannot be resolved.
- The anesthesiologists determine that the participant is at risk of hypoxemia or other life-threatening conditions.
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who signed the informed consent form (ICF) and subsequently withdraw, or discontinued from the study, will not be replaced.

7.3 LOST TO FOLLOW-UP

Not applicable in this study.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

During the study visit 2 (Day 1), the breathing sound and partial pressure of CO_2 will be recorded using the device with Airmod and Capnostream™35 respectively. The breathing sounds is obtained from the device with Airmod as a wav file, while the partial pressure of CO_2 (with sampling rate of 20 Hz) is obtained from Capnostream™35 as a txt file.

Accurate time frame is required as is the factor which may affect the endpoint. Both devices should start and end the recording at the same time in a specific time point, as below.

- Non-Anesthesia Stage: Up to 40 patients will be randomly assigned to non-anesthesia stage assessment, the measurement will be evaluated after enrollment with ICF, at the NOR area. (5~30 minutes)
- Procedure Stage: From firstly anesthetic administration to end of procedure. (Depends on procedure 10mins ~ few hours)
- NORA stage: From transportation of subjects to PACU to discharge from PACU (PAR or PADSS score ≥ 9) (Ideally keep following to 15 minutes)
    - Post Anesthesia Recovery (PAR) score

The information of patient monitoring period refers to 10.2.1.

The Post Anesthesia Recovery (PAR) score (Miller's Anesthesia, 9th Edition) will be performed and recorded by relevant personnel after the transfer of care through the PACU. Subjects are evaluated upon admission and every 15 minutes until a score of ≥ 9 is reached. Elements include:

Activity	Muscle activity is assessed by observing the ability of the patient to move his/ her extremities spontaneously or on command.
Respiration	Respiratory efficiency evaluated in a form that permits accurate and objective assessment without complicated physical tests.
Circulation	A measurement of cardiovascular homeostasis and a comparison with previous blood pressures.
Consciousness	Determination of the patient's level of consciousness.
Oxygen saturation	Measurement of arterial oxygen saturation using pulse oximetry.

- Post Anesthesia Discharge Scoring System (PADSS)

The Post Anesthesia Discharge Scoring System (PADSS) (Miller's Anesthesia, 9th Edition) will be performed and recorded by relevant personnel after the transfer of care through the PACU. Subjects are evaluated upon admission and every 15 minutes until a score of ≥ 9 is reached. Elements include:

Vital signs	A measurement of cardiovascular homeostasis and a comparison with previous blood pressures.
Activity level	Prior to discharge home, the patient's activity level must be at baseline. Patient must be able to ambulate at preoperative level.
Nausea and vomiting	Prior to discharge, the patient must have minimal to no nausea and vomiting.
Pain	Pain/discomfort must be at a level identified by the patient as tolerable. The location, type and intensity of pain should be consistent with anticipated postoperative discomfort.
Surgical bleeding	The surgical site must be free from excessive or unexpected bleeding/ drainage.

The breathing sounds and the partial pressure of CO_2 will then convert to the breathing counts and CO_2 waveform respectively using self-developed software written from Python and Matlab, the data will be recorded in Microsoft Excel and RR will eventually be calculated manually by trained personnel for each result.

During the study, if the study staff indicates the breathing sounds or the partial pressure of CO_2 is affected, for instance, an obviously external sound, moving the patient, nasal cannula drop, blocked, or other situation identify by the investigator. Such start/stop time of event(s) will be recorded in CRF, accurate to second. Such affected data or missing data will be excluded in the final comparison as such event(s) may be affecting the study result, determined by the investigator during the monitoring period.

8.2 SAFETY AND OTHER ASSESSMENTS

- Safety Assessment

The adverse events will be reviewed and evaluated by investigator throughout the study period (after enrollment to end of study). All adverse events will be recorded on the CRF.

- Medical History

A complete medical history will be reviewed at Screening. Medical history within 3 months prior to Screening will be recorded. Medical conditions occurring more than 3 months prior to Screening will not be recorded, unless they are judged by the principal investigator(s) to be significant.

- Demographic Data

Demographic information for each participant, including birth date and gender will be collected and recorded at Screening.

- Physical Examination

A full physical examination will be performed at Screening. Items will include: general appearance, weight and height, HEENT (head, eyes, ears, nose, and throat), mouth, skin, neck (including thyroid), lymph nodes, spine, cardiovascular system, respiratory system, gastro-intestinal system, nervous system, musculoskeletal system, blood and blood forming organs, mental status, and other body systems if applicable for describing the status of participant's health.

- Vital Signs

Vital signs include body temperature (°C), blood pressure (including systolic and diastolic blood pressure, unit: mmHg), and pulse rate (times/minute) will be performed at Screening. Results will be documented in the CRF. Vital signs should be evaluated after the participant has rested in a sitting position for at least 3 minutes. Note that study site staff should measure ear temperature of the participant if possible. If tympanic or axillary methods are used, the same method should be used consistently throughout the study.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Primary Analysis:

In this study, all the measurements were conducted in the same subject, and the clocking variance would be limited by investigator justification procedure to acquire the utmost matching recording. The study design is a paired non-inferiority test to evaluate accuracy and performance of respiratory rate (RR) measurement from Airmod compared to Capnostream™35. The primary objective is to establish the non-inferiority. The primary end goal is to test the entire effect at the margin of 3 breaths per minute (bpm). The non-inferiority is a directional (one-sided) test. The null hypothesis (H0) and alternative (H1) are defined as:

H0: μAirRR- μManCRR < -3 ;
H1: μAirRR- μManCRR ≥ -3.

Details refer to the SAP.

9.2 SAMPLE SIZE DETERMINATION

By referencing predicate device clinical trials on respiratory rate monitoring in the hospital setting, most of the cases recruited 120+ patients. Considering a 40% withdrawal/dropout rate, we proposed a total enrollment of 300 subjects.

Details refer to the SAP.

9.3 POPULATIONS FOR ANALYSES

The analysis will test the performance and safety using the Per-Protocol (PP) and Intention-to-Treat (ITT). The PP population is defined to be evaluable subjects who complete the entire study procedure without major protocol violations. The ITT population is defined to be all treated subjects who are administered using the device with Airmod and Capnostream™35.

Details refer to the SAP.

9.4 STATISTICAL ANALYSES

Details refer to the SAP.

9.4.1 GENERAL APPROACH

For descriptive statistics, continuous variables will be presented as N, mean, median, SD, maximum and minimum, while categorical variables will be presented as N and percentiles.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

In this study, all the measurements were conducted in the same subject, and the clocking variance would be limited by investigator justification procedure to acquire the utmost matching recording. The study design is a paired non-inferiority test to evaluate accuracy and performance of respiratory rate (RR) measurement from Airmod compared to Capnostream™35. The primary objective is to establish the non-inferiority. The primary end goal is to test the entire effect at the margin of 3 breaths per minute (bpm). The non-inferiority is a directional (one-sided) test. The null hypothesis (H0) and alternative (H1) are defined as:

H0: $\mu AirRR - \mu ManCRR < -3$;
H1: $\mu AirRR - \mu ManCRR \geq -3$.

At the interim analysis, under 99.69% CI, when reject the null hypothesis (H0) indicates the non-inferiority.
At the final analysis, under 95.1% CI, when reject the null hypothesis (H0) indicates the non-inferiority.

A subgroup analysis for those subjects with BMI ≥ 30 will follow the original study design in a stratified sample pool to test the non-inferiority at the margin of 3 bpm.

According to 7.2, part of the measurement result within subject will be censored and excluded in the paired non-inferiority test. The principle of exclusion is based on the investigator reported failure event/period of Airmod or Capnostream™35, the report will be confirmed by the principal investigator. The data prior to discontinuation or following a fixed machine failure period will be included in the paired non-inferiority test.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

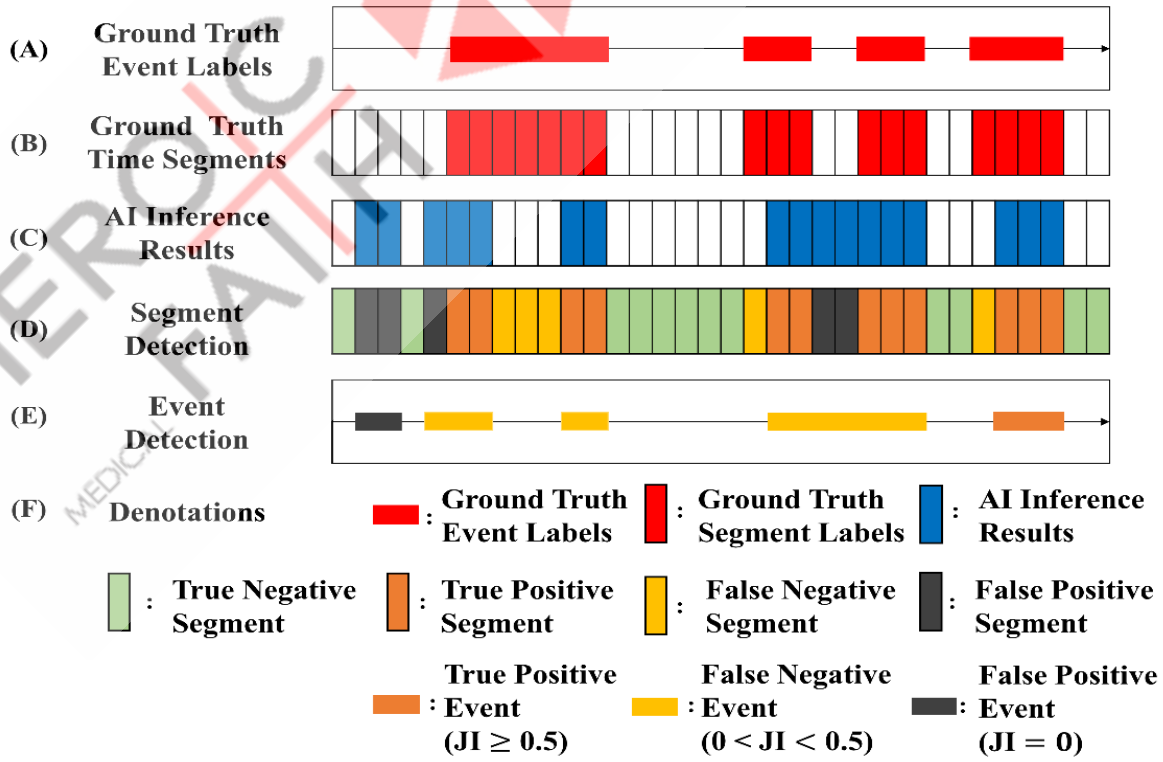
1. To assess the accuracy of respiratory rate measurement by Airmod in comparison with manual-scored auscultation sound during the less sensitive period of Capnography on Capnostream™35, the accuracy of inhalation classification in the segmentation basis is greater than 82.5% at the 95% CI. The performance metrics (F1-socre, MAPE) at event level will be demonstrated and target for F1-score > 0.8, MAPE < 0.5.
The precision and recall rate of Airmod deep learning machine, the F1-score build up and bind the hierarchy positive and negative metrics all together. It is generally described the harmonic mean of the two. Besides, the MAPE enhanced the difference power of error prediction by keep positive and negative errors from cancelling out each other. The relative errors are independent with the scale of target.

F1-score:

$$F-score = \frac{(1+\beta^2)\, precision \times recall}{\beta^2\, precision + recall}$$

MAPE:

$$\text{MAPE} = \frac{1}{n}\sum_{t=1}^{n}\left|\frac{A_t - F_t}{A_t}\right|$$



The output size of our model is a 235 x 1 vector for a 15-second audio recording so that the duration of each time frame is about 0.064 second. During the inference process, the deep learning model determines whether a time frame belongs to an inhalation. After comparing the inference results with the manual-scored ground-truth labels, we can assign true positive (TP), false positive (FP), true negative (TN), or false negative (FN) to each time frame. Thus, the accuracy ((TP+TN)/(TP+TN+FP+FN)) of inhalation detection in the segment level can be calculated. We use the accuracy of segment detection to evaluate the performance of the deep learning model.

2. To measure the agreement of AirRR and ManCRR on concordance correlation coefficient, and on their mean and bias by Bland-Altman analysis.
Bland-Altman analysis is used to measure the consistency of continuous data from two distinct measurements. Therefore, the likelihood of AirRR and ManCRR will be quantified and visualized on the assumption of fixed observer and pairs Bland-Altman analysis. It combines the quantitative analysis of LoA (limits of agreement) and the qualitative analysis of scatter plot to show an instinctive evaluation between two methods of their correlation. Each of the n samples is then represented on the graph by assigning the mean of the two measurements as the x-value, and the difference between the two values as the y-value. By this graphical method, we can extend a simple logarithmic transformation approach to data where there is a relationship between difference and magnitude. We discuss the importance of repeatability of RR measurements from each equipment and compare an estimate of this to the LoA. [20] In this case, if the difference of RR measured from two equipment are in the 95% LoA, we will say that RR measured from these two equipment are correlated and acceptable.

$$S(x,y) = \left(\frac{\Delta G\_A + \Delta G\_E}{2}, \Delta G\_A - \Delta G\_E\right)$$

3. Use paired t-test to compare the response time of Airmod versus Capnography on Capnostream™35 after administration of jaw thrust. In the target of p<0.05 indicates significance. The principal investigator and research members will determine the apnea period and the first effective breath.
The paired t test can be used when the two groups under comparison are dependent on each other. [21] By acquiring the T value from paired t-test, we can obtain the p value indicating the significant difference level via t-distribution table or Microsoft Excel. A p value less than 0.05 would indicate that Airmod is able to resume RR estimation after proper intervention faster than Capnostream™35.

$$t = \frac{\bar{X}_1 - \bar{X}_2}{\sqrt{\frac{(s_1^2 + s_2^2)2\rho s_1 s_2}{n}}}$$

4. Capnography is inherently limited in certain circumstances which may cause ineffectively detecting CO2, including movement, nasal cannula drop, blocked, or other situations. Airmod is superior to capnography in these limitations since it detects and measure breath sound directly.

4.1 The difference of ManCRR minus AirRR and ManCRR minus CapRR indicates non-inferiority at margin of 3 bpm (M1) and sampling rate 1Hz.

The difference between ManCRR and AirRR is comparing with the difference between CapRR and ManCRR to indicate the bias of Airmod are non-inferior to the reference devices at the margin of 3 bpm, which also demonstrates substantial equivalence.

4.2 The difference of ManCRR minus AirRR and ManCRR minus CapRR indicates non-inferiority at margin of 2 bpm (M2) and sampling rate 1Hz.

To evaluate whether Airmod can approach a strict standard suggested by clinicians, the difference between ManCRR and AirRR is comparing with the difference between CapRR and ManCRR to indicate the bias of Airmod are non-inferior to the reference devices at the margin of 2 bpm, which indicates the largest clinically acceptable difference.

According to 7.2, part of the measurement result within subject will be censored and excluded in the paired non-inferiority test. The principle of exclusion is based on the investigator reported failure event/period of Airmod or Capnostream™35, the report will be confirmed by the principal investigator. The data prior to discontinuation or following a fixed machine failure period will be included in the paired non-inferiority test.

5. The usability questionnaire as reference [Usability_Airmod] and descriptive analysis will be performed and recorded.

9.4.4 SAFETY ANALYSES

All candidates who were subjected to the device with Airmod and Capnostream™35 will be included in the safety analyses (performed in the Safety population) and data will be summarized using descriptive statistics. By reporting the numbers of adverse events (AE)/severe adverse events(SAE) within the trial to indicate the incidence rate of safety issues. We will also present the total number of patients suffering from AE/SAE and its percentage of all population.

The incidence of adverse events will be tabulated, summarized by intensity and relationship to the investigational product.

Details refer to the SAP.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Demographic data, physical examination, vital signs, the administered anesthetic medication and dosage, surgery type, start and stop time of surgery will be summarized. For continuous demographic variables, results will be summarized and presented as N, mean, SD, median, and minimum and maximum values. For categorical (nominal or ordinal) variables, the number and percentage of subjects will be used. No statistical testing will be performed.

9.4.6 PLANNED INTERIM ANALYSES

In the non-blinded total of 300 subjects enrolled, the interim analysis will be performed at the enrollment of 150 subjects (at least 30 non-anesthesia patients enrolled) during the study period. at the nominal significance level using OBrien-Fleming to determine α=0.00153. The final analysis will be performed at the end of 300 subjects enrolled. The nominal significance level is using OBrien-Fleming to determine α=0.02450.

9.4.7 SUB-GROUP ANALYSES

The primary endpoint will be analyzed based on different subgroups; details are described on SAP.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

No individual participant data will be listed by measure and time point.

10 SUPPORTING DOCUMENTATION

10.1 ABBREVIATIONS

AE	Adverse Event
AirRR	Airmod-scored auscultation sound generated from AS-101
BMI	Body Mass Index
bpm	breaths per minute
CapRR	Machine-scored Capnography (CapRR) generated from CapnostreamTM35 (K150272, Medtronic)
CE	Communate Europpene
CFR	Code of Federal Regulations
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DBP	Diastolic Blood Pressure
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
EMS	Emergency Medical Service
EtCO2	End-tidal Carbon Dioxide
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practices
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IP	Investigational Product
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITT	Intention-To-Treat
IVG	Intravenous General Anesthesia
LOA	Limits of Agreement
MHLW	Ministry of Health, Labour and Welfare
ManARR	Manual-scored auscultation sound originated from AS-101
ManCRR	Manual-scored Capnography (ManCRR) originated from CapnostreamTM35 (K150272, Medtronic)
NOR	Non-operating Room
OR	Operating Room
PACU	Post Anesthesia Care Unit
PADSS	Post Anesthetic Discharge Scoring System
PAR	Post Anesthetic Recovery
PI	Principal Investigator
PMDA	Pharmaceutical and Medical Devices Agency
PP	Per Protocol
QC	Quality Control
RMSD	Root Mean Square Difference
RR	Respiratory Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SoA	Schedule of Activities
SOP	Standard Operating Procedure
TFDA	Taiwan Food and Drug Administration
USADE	Unanticipated Serious Adverse Device Effect
US	United States
WMA	World Medical Association

10.2 SUPPLEMENTARY

10.2.1 PATIENT MONITORING PERIOD (TIME FRAME)

Device installation is done in the preparation period and trial will start upon sedation until discharge from the post-anesthesia care unit (PACU). A small group of patients (at least 40 patients) will also be evaluated for 15 to 30 minutes prior sedation or past discharge.

Location	Preanesthesia Evaluation	Preprocedural Patient Preparation	Sedative/Analgesic medication induction	Intraoperation	Post anesthesia care unit (PACU)
OR	Enrollment	Device installation / Preparation	Trial period[1*]	Trial period	Trial period[2*]
NORA	Enrollment	Device installation / Preparation	Trial period[1*]	Trial period	Trial period[2*]
Location	**Preanesthesia Evaluation**	**Non-anesthesia state**			**Eligible to discharge**
Prep room, PACU	Enrollment (40)	Device installation and Trial period for 15~30 minutes			Device installation and Trial period for 15~30 minutes

1* Notice : We included sedative/analgesic medical intended for general anesthesia and not intended for general anesthesia.

2* Notice : We followed the guidance that Patients receiving moderate procedural sedation may continue to be at risk for developing complications after their procedure is completed. Slow drug elimination may contribute to residual sedation and cardiorespiratory depression during the recovery period. Therefore, we proposed to track the recording until patient for fill the discharge requirement.

10.2.2 STUDY POPULATION

The population will be consisted with the study, to cover a wide range of health conditions, comorbidity, and risk, we proposed to enroll at least 40 non-anesthesia patients in a total of 300 sedative/ anesthesia patients from pre-anesthesia evaluation clinics.

10.2.3 INCLUSION CRITERIA

The compared digital stethoscope, AS-101, is not limited to patient age.

We will include patients eligible for procedure sedation/analgesia and have the target level from minimal to moderate and deep sedation/ analgesia. The enrolled patients' pre-anesthesia evaluation (followed ASA guidance) and their medical history will be recorded. We will also ensure that the patient group is wide enough to cover various common medical disorders.

Table 1. Continuum of Depth of Sedation, Definition of General Anesthesia, and Levels of Sedation/Analgesia

	Minimal Sedation (Anxiolysis)	Moderate Sedation/Analgesia (Conscious Sedation)	Deep Sedation/Analgesia	General Anesthesia
Responsiveness	Normal response to verbal stimulation	Purposeful* response to verbal or tactile stimulation	Purposeful* response after repeated or painful stimulation	Unarousable, even with painful stimulus
Airway	Unaffected	No intervention required	Intervention may be required	Intervention often required
Spontaneous ventilation	Unaffected	Adequate	May be inadequate	Frequently inadequate
Cardiovascular function	Unaffected	Usually maintained	Usually maintained	May be impaired

Minimal Sedation (Anxiolysis) indicates a drug-induced state during which patients respond normally to verbal commands. Although cognitive function and coordination may be impaired, ventilatory and cardiovascular functions are unaffected. Moderate Sedation/Analgesia (Conscious Sedation) indicates a drug-induced depression of consciousness during which patients respond purposefully* to verbal commands, either alone or accompanied by light tactile stimulation. No interventions are required to maintain a patent airway, and spontaneous ventilation is adequate. Cardiovascular function is usually maintained. Deep Sedation/Analgesia is a drug-induced depression of consciousness during which patients cannot be easily aroused but respond purposefully* after repeated or painful stimulation. The ability to independently maintain ventilatory function may be impaired. Patients may require assistance in maintaining a patent airway, and spontaneous ventilation may be inadequate. Cardiovascular function is usually maintained. General Anesthesia is a drug-induced loss of consciousness during which patients are not arousable, even by painful stimulation. The ability to independently maintain ventilatory function is often impaired. Patients often require assistance in maintaining a patent airway, and positive pressure ventilation may be required because of depressed spontaneous ventilation or drug-induced depression of neuromuscular function. Cardiovascular function may be impaired.

Because sedation is a continuum, it is not always possible to predict how an individual patient will respond. Hence, practitioners intending to produce a given level of sedation should be able to rescue patients whose level of sedation becomes deeper than initially intended. Individuals administering Moderate Sedation/Analgesia (Conscious Sedation) should be able to rescue patients who enter a state of Deep Sedation/Analgesia, whereas those administering Deep Sedation/Analgesia should be able to rescue patients who enter a state of General Anesthesia. (Developed by the American Society of Anesthesiologists: Approved by ASA House of Delegates on October 13, 1999 and last amended on October 15, 2014. Available at: http://www.asahq.org/quality-and-practice-management/practice-guidance-resource-documents/continuum-of-depth-of-sedation-definition-of-general-anesthesia-and-levels-of-sedation-analgesia. Accessed on August 21, 2017.)

*Reflex withdrawal from a painful stimulus is NOT considered a purposeful response.

10.2.4 EXCLUSION CRITERIA

Patients with advanced airway management equipment will be excluded. (For instance, Supraglottic airway device, LMA, Endotracheal tube.)

Some equipment, such as High Flow Nasal Cannula (HFNC), CPAP, suction machine, could continually make noise in the patient's airway, affecting auscultation and RR measurement. These conditions will also be excluded.

10.2.5 INTENDED FOR USE

The Airmod is an Android based software intended to be used with a legally marketed digital stethoscope as input sensor for the continuous, non-invasive monitoring of respiratory rate (RR) in patients aged 20 years and older who are subjected to procedural sedation in which the depth of sedation ranges from minimal to moderate and deep sedation/anesthesia. It is intended for use by healthcare professionals in hospitals and healthcare facilities performing procedural sedation/anesthesia.

10.2.6 SAP ABSTRACT

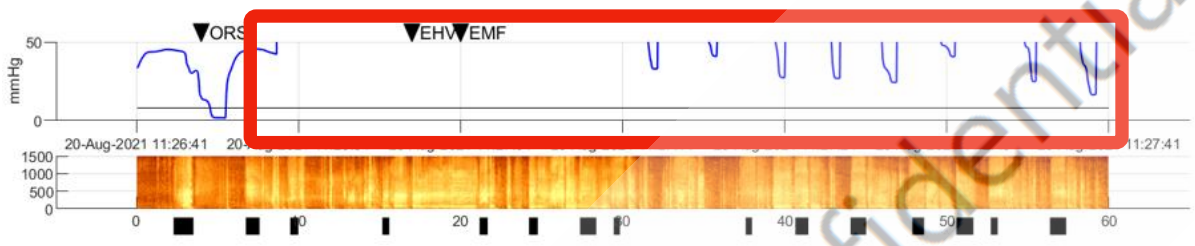
The primary objective is evaluating the non-inferiority of Airmod to Capnostream™35 for respiratory rate monitoring and user experience clinical evaluation, these results will be included in the clinical study report. In a total of 300 patients enrolled, Airmod and Capnostream™35 recorded the respiratory rate concurrently. The demographic of patients and their Charleson comorbidity in the statistical analysis are collected to describe the patient population in our study. We will further analyze the primary and secondary end goal in the records to show non-inferiority of respiratory rate estimation, agreement, and the excellence event detection of Airmod to Capnostream™35. The subgroup analysis in each period and particular BMI patient group will indicate the statistical power of our study and provide further information on the substantial equivalence performance in

respiratory rate measurement. We will also record all the adverse events during the procedure for analysis of device-related hazards or adverse events for the submission documents.

10.2.7 EXAMPLES OF EXCLUDED MEASUREMENT

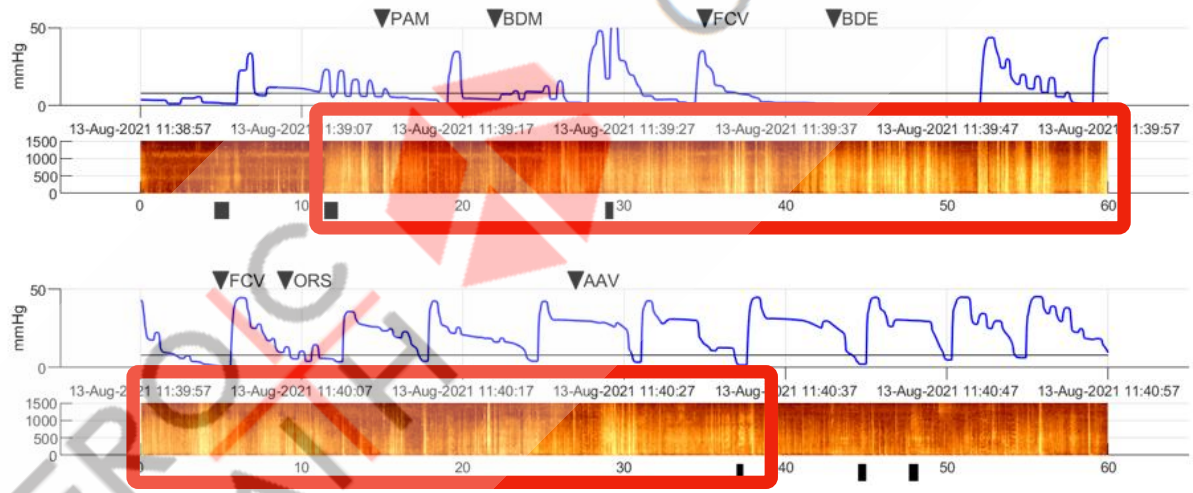
The principle of exclusion is based on the failure event/period of Airmod or Capnostream™35 reported by investigator. Events such as EtCO2 oversaturated period of Capnostream™35 or noises unable to be eliminated by the noise-cancelling technology and bias the respiratory rates. The report will be confirmed by the principal investigator, data apart from these events is still included.

EtCO2 oversaturated period of Capnostream™35:



*ORS: Operation start; EHV: Patient exhausting voice; EMF: Capnostream™35 failure determined by Investigator

Noises unable to be eliminated by the noise-cancelling technology and bias the respiratory rates:



*PAM: Patient movement; BDM: Sickbed movement start; FCV: Friction voice; BDE: Sickbed movement end; AAV: Abnormal acoustic sound produced by upper GI endoscope.

10.3 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
3.0	2021/10/1	Minor fixed of description (no effect with study design) and added supplementary section (10.2).	Found some description errors (no effect with study design). Meanwhile, give further information to complement the protocol.

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