A Comparison of Capnography Sampling Lines Trial

NCT03554629

- Clinical Investigation Plan (CIP), version 2 dated 01 June 2018

Medtronic

Clinical Investigation Plan

Clinical Investigation Plan/Study Title	A Comparison of Capnography Sampling Lines
Clinical Investigation Plan Identifier	MDT17063FRS
Document Version	2. 0 30MAY2018
Sponsor	Medtronic/Covidien LP, a Medtronic company MITG Respiratory, Gastrointestinal & Informatics (RGI) 6135 Gunbarrel Avenue Boulder, Colorado 80301
Lead Principal Investigator	Thomas A. Minor MD Pulmonologist/Sleep Medicine Clinimark, LLC 80 Health Park Drive, Louisville, CO 80027

1. Investigator Statement

Sponsor	Medtronic/Covidien LP, a Medtronic company MITG Respiratory, Gastrointestinal & Informatics (RGI) 6135 Gunbarrel Avenue Boulder, Colorado 80301
Clinical Investigation Plan Identifier	MDT17063FRS
Version Number/Date	2.0/30MAY2018

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated. I agree to comply with International Conference on Harmonization Guidelines on Good Clinical Practice and United Stated Food and Drug Administration regulations 21 CFR 50, 21 CFR 56, 21 CFR 54 and 21 CFR 803.
I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation and conduct of the clinical investigation without the prior written consent of Medtronic.
I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Medtronic. I will discuss this material with them to ensure that they are fully informed about the products and the study.

Investigator's Signature:	Signatures Held in the
Investigator's Name:	Study Trial Master File
Institution:	(TMF) at Medtronic
Date:	

Table of Contents

2. Glossary

Term	Abbreviation	Definition
Adverse Event	AE	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether related to the medical device. Note: This definition includes events related to the medical device or the comparator. Note: This definition includes events related to the procedures involved. Note: for users or other persons, this definition is restricted to events related to the medical devices.
Adverse Device Effect	ADE	Adverse event related to the use of a medical device. Note: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation or any malfunction of the medical device. Note: This definition includes any event resulting from use error or from intentional misuse of the medical device.
Carbon Dioxide	CO2	CO2 is a colorless and odorless gas that is a by-product of animal cellular metabolism removed by the lungs in exhaled gas and can be measured by capnography during the respiratory cycle.
Capnography	CO_2 monitoring	Continuous, non-invasive measurement and monitoring of carbon dioxide concentration of the expired and inspired breath and a function of time and respiration rate based the carbon dioxide respiration cycle.
Capnostream®35	CS35	The Capnostream®35 combined capnography/pulse oximeter monitor and its accessories are intended to provide professionally trained health care providers with continuous, non-invasive measurement and monitoring of carbon dioxide concentration of

Term	Abbreviation	Definition
		the expired and inspired breath and respiration rate, and with continuous non-invasive monitoring of functional oxygen saturation of arterial hemoglobin (SpO_2) and pulse rate. The CS35 contains many FDA cleared smart algorithms such as IPI and ASA.
CO_2 cannula sampling filterline	CCSF	Products under study with variation on patient interface cannula designs to secure a breath gas sample to the capnography device for measurement of the partial pressure of CO_2 in the breath gas mixture.
End Tidal CO_2	$EtCO_2$	The numeric partial pressure of the maximum value of carbon dioxide in the exhaled breath over the last 20 seconds. The $EtCO_2$ numeric value is updated once a second. Alternative abbreviations used in the literature are $ETCO_2$ and $etCO_2$.
Fractional inspired carbon dioxide	$FiCO_2$	The numeric partial pressure of carbon dioxide present during inhalation.
Nasal Cannula	NC	Nasal prongs in the nares for gas sampling and/or oxygen delivery
Non-invasive ventilation	NIV	Noninvasive ventilation (NIV) refers to the administration of ventilatory support without using an invasive artificial airway (endotracheal tube or tracheostomy tube).
Nare		The nose nostril airway.
Oxygen	O_2	A colorless, odorless gas that provided to the body via inhalation and is required for metabolic creation of energy to sustain life.
Pulse Oximetry	SpO_2	Depends on pulsatile blood flow and measures only the oxyhemoglobin in arterial blood as it leaves the heart.
Respiration Rate	RR	The count of breaths per minute based upon the carbon dioxide cycle as measured by capnography.
Septum		The osseo-cartilaginous midline structure in the nose that divides the now into two (2) similar halves.
Serious Adverse Device Effect	SADE	Adverse device effect that has resulted in any of the consequences characteristic of a Serious Adverse Event.
Serious Adverse Event	SAE	Adverse event that 1. led to death,

Term	Abbreviation	Definition
		2. led to serious deterioration in the health of the subject, that either resulted in a. a life-threatening illness or injury, or b. a permanent impairment of a body structure or a body function, or c. in-patient or prolonged hospitalization, or d. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, 3. led to fetal distress, fetal death or a congenital abnormality or birth defect Note: Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event.

3. Synopsis

Title	**A Comparison of Capnography Sampling Lines**
Clinical Study Type	**Interventional Comparative Study**
Product Names	Study carbon dioxide (CO_2) cannula sampling filterline (CCSF) disposable products with variations on the cannula patient interface designs all FDA cleared 1. Medtronic (MDT) Microstream™ CO_2 FilterLine™ nasal cannula 2. Salter Labs® nasal cannula 3. Hudson RCI®/Teleflex® nasal cannula 4. flexicare® nasal cannula 5. Westmed oral nasal cannula 6. DispoMed® oral nasal cannula with reflective monitor end connection 7. Medtronic (MDT) Microstream™ CO_2 FilterLine™ oral nasal cannula 8. Salter Labs® oral nasal cannula Note details of product name and 510K numbers is in Section 7.1
Sponsor/Local Sponsor	Medtronic/Covidien LP, a Medtronic company MITG Respiratory, Gastrointestinal & Informatics (RGI) 6135 Gunbarrel Avenue Boulder, Colorado 80301
Indication under investigation	A CO_2 cannula sampling filterline (CCSF) is designed to collect breath gas samples via the cannula interface from the nose or nose and mouth. The gas sample is sent to a capnography monitor for CO_2 partial pressure measurement in millimeters (mm) of mercury (Hg). There are many variations on the cannula patient interface design. The Medtronic Microstream™ CO_2 FilterLine™ cannula sampling lines (Microstream™ CCSF) are designed for use with Microstream™ enabled

	capnography monitors to capture quality breath samples without effecting CO_2 measurement when supplemental O2 flow up to 5 liters/minute. All the cleared CCSF products under study will be used within the approved intended use.
Investigation Purpose	To collect CO_2 measurements on human subjects as a function of the carbon dioxide (CO_2) cannula sampling filterline (CCSF) during simulated patient activity to provide guidance on filterline selection in the clinical setting for Microstream™ enabled monitors. There is no human data on variations of CCSF performance to provide an adequate breath sample when connected to the Microstream™ enable monitor.
Product Status	All devices are USA FDA Cleared products and will be used within the intended use.
Primary Objective(s)	To compare the performance of the Medtronic Microstream™ FilterLine™ compared to the non-Medtronic CCSF products during predefined expected patient activities to provide a quality sample of breath gas to the Microstream™ enabled capnography monitor.
Secondary Objectives(s)	To score non- Microstream™ CCSFs performance against the Medtronic (MDT) Microstream™ FilterLine™ performance.
Study Design	Prospective, Interventional, Single Center, comparative product study on a convenience sample of out-of-hospital volunteers. Subject enrollment not to exceed 3 hours of study procedure participation. No follow-up is required.
Randomization	Subjects are not randomized to any treatment or procedure group.
Sample Size	Up to 50 consented subjects at one clinical site in USA to secure a minimum of 30 complete subject data sets. A subject may be re-consented to collect data on the two additional CCSF that have been added to this version of the CIP. These re-consented subjects will not be included in the total sample size of 50.
Inclusion/Exclusion Criteria	Inclusion: 1. Non-hospitalized adults ≥ 18 years old. 2. Willing and able to give informed consent. Exclusion: 1. Lack of an informed consent. 2. Subjects not able to accommodate the proper application of the cannula. 3. Subject not willing or able to comply fully with the study procedures. 4. Subjects with sensitivity to nasal cannula in both nares. 5. Subject with skin allergies to medical adhesives. 6. Subjects with runny nose the day of the study participation. 7. Subject, who in the opinion of the Principal Investigator, should not be enrolled.

Study Procedures and Assessments	The sequence of the carbon dioxide (CO_2) cannula sampling filterlines (CCSF) disposable products under test for the sequential scripted activities will be randomized by subject ID. The Procedure scripted activity case report form (CRF) record with and without Supplemental O_2 may include: 1. Variation of mouth position (open/close) 2. Partial and full unilateral nasal obstruction by subject finger as directed 3. Oral/ nasal shifting pattern with variations of mouth position. 4. Variation in respiratory effort and rate 5. Variation of head position 6. Body position changes (sitting, standing, lying on a bed) The above CRF procedure list of potential scripted activities may not extend beyond the three hours of consented enrollment. With the three-hour limit on subject enrollment, the targeted list of scripted activities will be prioritized in terms of those activities that would most likely lead to sampling difficulties as per PI/Sub-I in consultation with MDT. The initial list of scripted activities maybe reduced after the high frequency measured device data is collected and reviewed on an ongoing basis on the first 5 up to 10 subjects to eliminate those activities that provide no significant differences in sampling performance without a much larger sample size. Scripted activities will not be added to the CRF only removed.
Safety Assessments	Subjects will be monitored for Adverse Events, Serious Adverse Events, and Device-Related Adverse Events continuously during study execution by the Study Coordinator via visual and verbal assessment of the subject and observation of device data notifications on measured non-invasive arterial oxygen saturation (SPO_2).
Statistics	Statistical analyses will be conducted by Medtronic or its designee as outlined in the Statistical Analysis Plan (SAP). Any changes in statistical methods will be detailed in the SAP. Demographic information and baseline characteristics data will be summarized using descriptive statistics. Cross-over comparison of each CCSF design by subject and in aggregate using the endpoints will be used to meet the primary and secondary objectives. Multiplicity adjustments will be done using the method of Tukey-Kramer multiple comparisons.

4. Introduction

4.1. Background

The Medtronic (MDT) Microstream™ enabled monitors offer a unique and highly specific measurement technology using Molecular Correlation Spectroscopy™ (MCS™) for the measurement of the partial

pressure of carbon dioxide (CO_2) in any gas mixture. The technology has allowed for an extremely small sample cell (15 microliter) within the monitor, which in turn, permits the use of a very low sample flow rate (50 ml/min) for CO_2 partial pressure measurement. Capnography is the monitoring of the concentration or partial pressure of carbon dioxide (CO_2) in the respiratory gases. The peak CO_2 partial pressure during the respiratory cycle is at the end of expiration is called end tidal carbon dioxide ($EtCO_2$).

A key to obtaining an accurate $EtCO_2$ measurement and quality waveforms with any capnograph is the sampling line. Measurement technology can only report what is being delivered, so if the sampling line is not providing a representative CO_2 sample, the accuracy of the measurement is impacted. The MDT Microstream™ FilterLine™ designs are designed for use with Microstream™ enabled capnography monitors to capture quality breath samples for measurement with an integrated supplemental O_2 delivery design.

There is no human subject evidence on the performance of cleared non- Microstream™ CO_2 cannula sampling filterline (CCSF) designs when they are connected to the Microstream™ enabled capnography monitors.

There is one published manuscript on the performance of CO_2 sampling filterline cannula design with adult subjects at rest using on a non- Microstream™ capnography monitor and one publication on nasal cannula design in laboratory simulation.[1,2] Literature search on Ovid and PubMed failed to identity any additional published evidence on the performance of any CO_2 sampling filterline performance during expected patient activity such as variation of RR, variations of respiration patterns/efforts or positional changes when connected to any capnography monitor.

4.2. Purpose

The purpose of this study is to provide guidance on filterline selection in the clinical setting for Microstream™ enabled monitors. There is no human data on variations of CCSF performance to provide an adequate breath sample when connected to the Microstream™ enabled monitor.

[1] See Ebert, T; The Effectiveness **of** Oxygen Delivery **and** Reliability **of** Carbon Dioxide Waveforms**: A** Crossover Comparison **of** 4 Nasal Cannulae**.**

[2] See Marshall, G; Right Versus Left Prong Nasal Cannula Flow Delivery and the Effects of Nasal Cycling on Inspired FIO2 in an Adult Anatomic Model.

All the CCSF (CO_2 cannula sampling filterlines) in this comparative study were cleared by FDA with the integrated connection option for the provision of low flow supplemental oxygen.

The rational to conduct this study is the lack of human data on variations of CCSF performance to provide an adequate breath sample when connected to the Microstream™ enabled monitor.

This data collected in this study may guide filterline selection in a variety of clinical settings for Microstream™ enabled monitors.

5. Objectives and Endpoints

5.1. Objectives

5.1.1. Primary Objective(s)

The primary objective of this clinical study is to compare the performance of the Medtronic Microstream™ FilterLine™ compared to the non-Medtronic CCSF products during predefined expected patient activities to provide a quality sample of breath gas to the Microstream™ enabled capnography monitor.

The primary endpoints will be the frequency and duration of false physiological alarms, device notifications regarding a reduction in CO_2 Waveform device messages/notifications such as filterline blockage, performing auto zero, clearing the filterline and CO_2 error.

5.1.2. Secondary Objective(s)

The secondary objective is to score the performance of the non- Microstream™ CCSFs compared to the Medtronic (MDT) Microstream™ FilterLine™. The primary endpoints will be the foundation to score sampling performance per activity by subject and in aggregate.

The need to score performance by the scripted simulated patient activities will provide information on optimal filterline selection based upon end use clinical setting and expected patient activity.

6. Study Design

Prospective, interventional, single center, comparative product study design on a convenience sample of out-of-hospital volunteers. Intervention assignments (CCSF sequence) for each subject will be based upon a randomized sequence by subject ID. Subjects will serve as their own control within each of the repeated scripted activity periods (such as variations on mouth positions, partial and full unilateral nasal obstruction, nasal/oral respiration shifting pattern, variations in respiratory effort and rate, variations of head position, variations of body position) in the study design.

Subject consented enrollment will not exceed 50 to secure device data on up to 30 subjects. Subject enrollment will not exceed 3 hours of study procedure participation. If a subject is withdrawn before completing the study procedures, an additional subject will be recruited to obtain up to 30 subject complete device data sets. Enrollment will end when up to 30 complete subject data have been collected, transferred to Medtronic and device data is verified as valid. No study procedure follow-up is required.

The FDA cleared CO_2 cannula sampling filterline (CCSF) products for performance comparison when connected to the Medtronic Microstream™ vary in the patient interface cannula design for breath sampling from the nose or from the nose and mouth. The products will be used according to the manufacturer instructions for use to collect and provide a breath sample to a capnography monitor and will not be modified.

Each subject will wear up to eight (8) CO_2 cannula sampling filterline (CCSF) in a randomized block sequence for repeated targeted scripted activities with and without supplemental O_2 up to 5lpm with capnography device data collected. The prioritization of the scripted activities will be based upon physiological conditions that would contribute to challenging sampling of exhaled gas to keep enrollment time at less than 3 hours/day. The sequence of each of the 8 CO_2 sampling filterline cannula to be worn by each subject will be randomized by subject ID to reduce sequence bias. The low impact activities will not be randomized but a minute washout break between each activity will be included in the case report form to acquire baseline data. Due to the time limit it may be possible that not all 8 filterlines are utilized by each subject during enrollment.

During the study procedures, the study case report form will be used to record subject ID, randomization of cannula sequence assigned by subject ID and the CS35 device time for each activity to link procedure activity time to the timed electronic device data. The CS35 device data will be collected at 20 data points/second via a USB per the CS35 instructions for use with subject ID recorded in the device data file name.

Foreseeable factors that may compromise the outcome of the study include lack of recognizing and including patient activities that might affect breath sampling. Every effort was made to include activities known to effect sampling in the clinical environment.

6.1. Duration

The duration of the study for first enrollment to end of enrollment will be no more than eight months.

Each subject will be actively enrolled for study procedure for not more than three hours/day. With the update to the CCSF under test list, the six subjects that did not wear the two replaced filterlines (#5 and #6) will be re-consented and will undergo the study procedures for the 2 replaced filterlines that are introduced with this CIP version.

Subjects can be withdrawn without penalty and be compensated for their time at a rate of 37.50 USD per 30 minutes of enrollment in study procedures, as defined in Section 9.0

No follow-up for any subject is required for this study.

6.2. Rationale

There is a clinical need to understand the performance of non- Microstream™ CO_2 cannula sampling filterline (CCSF) designs to provide a representative quality respiration gas sample for monitoring of ventilation on a Microstream™ enabled capnography monitor in the clinical setting.

There is a need to provide a comprehensive guideline on CO_2 cannula sampling filterline selection in the clinical setting to include non-Microstream™ CCSF products for end-users of Microstream™ enabled monitors. The chosen study design was based on similar comparative human interface product design models where each subject serves as their own control with facial anatomy a constant by subject.

7. Product Description

7.1. General

Medtronic will provide the FDA cleared disposable CO_2 cannula sampling filterlines, pulse oximeter probes and the Capnostream® 35 (CS35) as the Microstream™ enabled monitor for use in this study along with the manufacturer instructions for use.

Below is a list of commercially available products that will be used in this study with manufacturer: product name/sampling method (K number):

A. Study carbon dioxide (CO_2) cannula sampling filterline (CCSF):

1. Medtronic (MDT) Microstream™ CO_2 FilterLine™: O_2/CO_2 FilterLine™ /nasal cannula(K010024)
2. Salter Labs®: ETCO2/O2 nasal sampling line/ one nare sampling cannula (K151421)
3. Hudson RCI®/Teleflex®: Softech® Bi-Flo ETCO2 Sampling Cannula/nasal cannula (K961150)
4. flexicare®: Dual Nare Nasal Cannula with O_2/CO_2 Combination Monitoring/ nasal cannula (K140113)
5. Westmed: Adult CO_2 /O_2 Oral/Nasal Cannula/ oral nasal(K162343)
6. Dispo-MED®: Nasal/Oral CO2 Sampling Cannula w/O_2 Delivery with reflective connection (K143127)
7. Medtronic (MDT) Microstream™: Smart CapnoLine™ Plus/oral nasal cannula(K010024)
8. Salter Labs®: Oral-Trac®/ oral nasal cannula (K151421)

B. Medtronic Nellcor™ SpO_2 Adhesive Disposable Sensors, Adult >30 kg, Max-A (K051271)

C. Medtronic Capnostream® 35 (CS35) a Microstream™ enabled capnography medical device (K150272).

7.2. Manufacturer

The Manufacturer of the cleared medical devices are listed above with the 510(k) numbers.

7.3. Packaging

The disposable CCSF products are single patient, packaged singly in non-sterile packaging with expiration date on use marked on the packaging. Supplied CCSF products provided for the study will not be beyond the expiration date if an expiration date is on the packaging.

The disposable Nellcor™ SpO2 Adhesive Sensors are single patient, packaged singly in non-sterile packaging with expiration data on use marked on the packaging. Supplied SpO2 sensors provided for the study will not be beyond the expiration date.

The Capnostream®35 (CS35) dual parameter portable monitor will be hand carried to the site and be in calibration for use.

7.4. Intended Population

The Capnostream™ 35 combined capnograph/pulse oximeter monitor and its accessories are intended to provide professionally trained health care providers with continuous, non-invasive measurement and monitoring of carbon dioxide concentration of the expired and inspired breath and respiration rate, and with continuous non-invasive monitoring of functional oxygen saturation of arterial hemoglobin (SpO_2) and pulse rate.

The required accessory to non-invasively measure of the partial pressure of CO_2 in the provided breath sample (ventilation) is a CO_2 cannula sampling filterline (CCSF) to be placed on the subject face. The variations of cannula design for breath sampling and delivery of supplemental oxygen are under investigation in this study.

The required accessory to non-invasively measure arterial oxygen saturation is a sensor to be wrapped around one finger.

7.5. Equipment

A. Microstream™ capnography enabled monitor

A calibrated CS35 dual parameter monitor (Figure 1) will be provided to measure capnography via the CO_2 cannula sampling filterlines under investigation and pulse oximetry. Should the CS35 device fail during the conduct of the study a new monitor will be provided. Failure history will be reported to Medtronic.

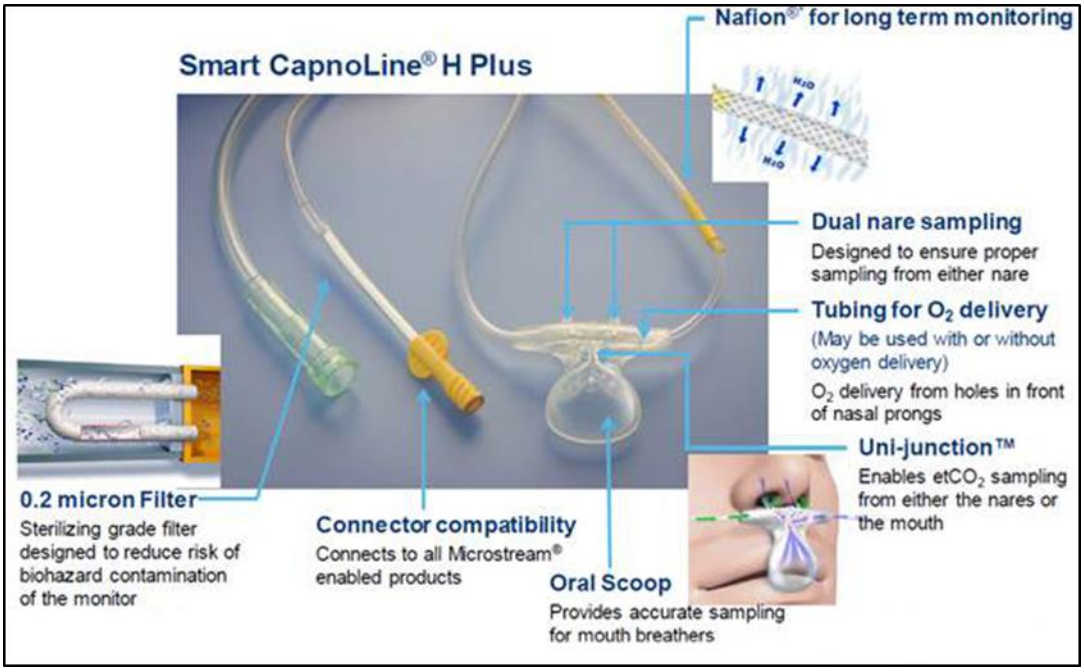
Figure 1. Capnostream 35

B. CCSF cannulas under investigation

Eight different CO2 cannula sampling filterlines will provided for investigation for quality of the breath sample provided. Figure 2, The Microstream™ CO_2 FilterLine™, provides a graphic of the long -term duration version of the Smart CapnoLine™ Plus which is one of the MDT reference cannula for comparison. The Non - Microstream™ CCSF designs are variation on sampling port(s) and supplemental O_2 delivery ports.

The inline Nafion® on the long duration version Smart CapnoLine™ Plus increases the duration of sampling use by managing the inline humidity (H) via water vapor diffusion. The absence or presence of the Nafion® does not compromise CO_2 gas partial pressure measurement in the Microstream™ enabled monitor.

Figure 2. Microstream™ Smart CapnoLine™ H Plus (H means humidity management)

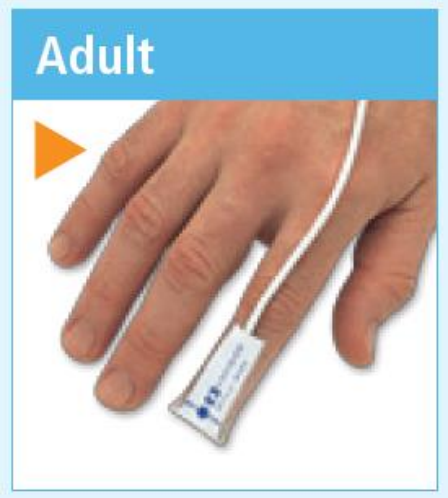


Any failure of the disposable CO2 cannula sampling (CCSF) device under investigation to measure CO_2 will be identified by the CS35 device electronic data which will also contain all device and alarm notifications with the time of the event. Any failure of a MDT medical device noted on the device deficiency log will be processed within MDT as a product complaint.

C. MDT Nellcor Max A disposable pulse oximeter finger sensor

Pulse oximetry finger sensor will non-invasively measure the amount of hemoglobin saturated with oxygen or SpO_2. Light emitting diodes (LEDs) emit red and infrared light. Changes in light absorption during the pulsatile cycle determine the SpO_2.

Figure 3. Medtronic Nellcor MAX A disposable pulse oximeter.



7.6. Product Use

Product provided to the site by the study sponsor is for study subject use only. Study use of the CS35 and the accessories (disposable CO_2 sampling filterlines and disposable SpO2 probes) will be according to the IFUs provided to Clinimark.

7.7. Product Training Requirements

Product information will be included in the study training material with hand-on use of the devices. The device data transfer process will be tested and verified during the site initiation process and training will be provide on transfer of the device data to MDT via an encrypted and password protect MDT Box site.

All the training material will be based upon the IFU with a focus on the study needs to collect device date with the accessories used as per IFUs. A copy of study medical device IFUs will be provided to the site prior to the IRB submission.

7.8. Product Receipt and Tracking

Shipment/delivery and receipt of all study medical devices and equipment provided per the contract will be tracked and signed records maintained in the MDT trial master file (TMF). The records will include dates, quantities, lots/serial numbers and equipment descriptions.

7.9. Product Storage

Storage of the cleared study product will reside at Clinimark and only be available to the study staff for study enrollment. Clinimark is an external physiological lab with restricted work hours and access.

7.10. Product Return

The return of the CS35 dual parameter monitor and unused disposable CO_2 sampling line will be documented on the MDT product Shipment Form with product details which includes product name, serial or Lot# and quantify returned. This record will be filed in the Medtronic TMF.

7.11. Product Accountability

The investigator will store the study product. The storage area should be locked/secure with access limited only to approved study staff. Devices will be stored at Clinimark LLC, a human performance laboratory with limited access within a hospital facility.

Records will be maintained of product delivery to the study site. This includes dates, quantities received, lot/serial numbers, and expiration dates if noted on the product packaging.

Use of the study device by each participant will be recorded in a device accountability log.

8. Selection of Subjects

8.1. Study Population

The target population consists of non-hospitalized volunteer subjects of adult age (≥18).

8.2. Subject Enrollment

Subjects will be considered enrolled once the informed consent has been signed. If a subject is withdrawn after signing the informed consent, the subject will be replaced by increasing the enrollment. The minimum number of subjects to be consented is 30 with a maximum of 50 with an expected withdrawal rate to 10%.

8.3. Inclusion Criteria

1. Non-hospitalized Adults ≥ 18 years old
2. Willing and able to give informed consent

8.4. Exclusion Criteria

1. Lack of an informed consent
2. Subjects not able to accommodate the proper application of the cannula
3. Subject not willing or able to comply fully with the study procedures
4. Subjects with sensitivity to nasal cannula in both nares
5. Subjects with skin allergies to medical adhesives
6. Subjects with a runny nose the day of the study participation
7. Subject, who in the opinion of the Principal Investigator, should not be enrolled.

9. Study Procedures

9.1. Schedule of Events

Study duration per subject is up to three hours with no study follow-up visits.

Data will only be collected on the enrollment visit unless a follow-up phone call is required to close an AE. Data collection requirements are summarized in Table 1. The study site personnel must report all study specific Adverse Events (AE) and changes in status of these Adverse Events from time of enrollment until the AE is closed by the Principal Investigator.

9.1.1. Enrollment Visit

The point of enrollment is when written informed consent is obtained after meeting criteria for enrollment. Removal from the study after consent will be considered a withdrawal.

Information for enrolled subjects will be captured on the Health Assessment section of the CRF Form.

Consent Process

1. Explain the procedure to the subject. Have them read the Informed Consent Form (ICF), and review the information answering all questions.
2. Assign a subject ID number and record that number on the CRFs and the enrollment log. Ask the subject to provide the information to complete the Health Assessment CRF for subject demographics, history of oral & nasal surgery, sleeping and/or breathing difficulties, sinus problems and inhalation medications.
3. Each subject will be given a copy of the signed ICF prior to leaving Clinimark.

Study Procedure Process

1. Have the subject sit comfortably.
2. Identify the sequence of the CCSF (CO_2 cannula sampling filterline) design sequence linked to the subject ID per the MDT CCSF sequence randomization table and obtain the CCSF products.
3. Setup the CS35 medical device and verify that the communication between the CS35 and the USB for electronic device data extraction is working via the CS35 messaging per the MDT study device training material. The USB device election data will leave Clinimark on an encrypted USB at the end of the study and be provided ongoing via the encrypted and password protected Box site. The device data will contain serial number of the device, date and time, subject ID and all the device measured physiological data with device notifications.
4. Enroll the subject ID into the CS35 device so the electronic data will be saved by subject ID with the date and device serial number as per the MDT study device training material.
5. Apply the assigned CO_2 sampling filterline cannula (CCSF) per randomization sequence.
6. Record the assigned CCSF code name (A – F) on the CRF printed activity list.
7. Adjust subject interface cannula as appropriate and record that the cannula was on properly.
8. Start CS35 electronic device data collection on USB per the data output menu on the CS35 and enter the CCSF code name as free test using the event marker. This electronic device data will be correlated to the CRF with the listed sequence of activities and posted time. It is essential to link the CRF to the electronic device data by time and CCSF code name for data analysis.
9. Record CS35 monitor start time for each scripted activity on the procedure CRF with the posted EtCO2 under the CCSF code name in current use. The scripted activities may include any of the following with or without supplemental O_2 up to 5lpm:
    A. Variation of mouth position (open/close)
    B. Partial and full unilateral nasal obstruction by subject finger as directed
    C. Oral/ nasal shifting pattern with variations of mouth position.
    D. Variation in respiratory effort and rate
    E. Variation of head position
    F. Body position changes (sitting, standing, lying on a bed)
10. Respiration rate will be coached using a metronome by the study staff and document if a subject is not in sync with the metronome.
11. The study staff will monitor the subject's well-being through-out the test confirming that the subject is doing ok and $SpO_2 \geq 90$. Should the subject's SpO2 drop below 85%, for a duration of 30 seconds, the study activities including the provision of supplemental O_2 will be paused as needed to maintain $SpO_2 > 90\%$. The purpose of the low flow supplemental O_2 provided in this study is to measure the effect on breath sample gas dilution and not as a treatment for subject low oxygenation.
12. Subject will be advised during the study that he/she may stop the test at any time.
13. The test may be stopped at any time by the subject, the clinician or study coordinator.
14. Once each activity has been performed, the subject will remove the CO_2 cannula sampling filterline with the CS35 monitor time recorded on the CRF with any comments on comfort or discomfort.
15. Repeat 5 – 14 until all the CCSF device interface models have been worn per the assigned sequence of activities not to exceed the three-hour limit and unless the study is terminated. There may be situations where not all 8 filterlines may be worn by each subject due to the time constraint. The activity list will be reduced over time in this adaptive CRF process such that only those activities that demonstrate difficulties in sampling in any CCSF device will remain.
16. All equipment will be removed from the subject.

A study coordinator will be with subject during enrollment and will determine subject compliance to the procedures. If a subject is not compliant, the subject will be withdrawn.

Table 1. Data Collection Requirements and Source

Data	Screening evaluation	Enrollment Visit, Study Procedures, Exit	After Day One Follow-up to close any open AEs	Source Document
Location	Phone using the Clinimark recruitment pool	Clinimark	Phone and Clinimark if required by PI	
Informed Consent		**X**		ICF at the Site
Inclusion/Exclusion Criteria Evaluation	X	X		Health Assessment CRF
Medical History and Demographic via the Health Assessment CRF		X		Health Assessment CRF -Self reported
Nasal Deviated Septum Self-Exam Score		X		Health Assessment CRF -Self reported
Adverse Events (AE)		X	X	AE CRF
CS35 Device Memory Data		X		USB
Device Deficiencies (DD)		X	**x**	DD CRF
Protocol Deviations (PD)		X	x	PD CRF

The list of CO_2 sampling cannula filterline under test to be used in an assigned CCSF code name randomized sequence by subject ID is in Section 7.1.

9.1.2. Study Exit

Before the subject is discharged from the study, the study coordinator/clinician will review any final questions with the subject and ask if there were any effects from the study. The subject will be released with no further follow up required.

9.2. Subject Screening

Subjects will be screened and recruited from the Clinimark volunteer recruitment pool meeting the criteria for enrollment in this study by phone.

9.3. Prior and Concomitant Medications

No restriction on existing medication and/or treatments before and/or during the study. If the subject is on a prescription aerosol inhaler (corticosteroid inhaler or bronchodilator) or uses non-invasive positive pressure ventilation (CPAP or other) at night that will be recorded on the Health Assessment Case Report Form (HACRF) after informed consent has been provided by the subject. A subject will provide self-reported information to complete the pre-procedure Health Assessment section of the CRF.

9.4. Subject Consent

The investigator or authorized designee must obtain written informed consent on subjects meeting the inclusion criteria and none of the exclusion criteria before any clinical study related activity takes place. Written informed consent must be obtained prior to participation in any procedure scripted activities.

9.5. Randomization and Treatment Assignment

There is no blinding or randomization to subject procedure. A Medtronic statistician will provide a cannula sequence randomization table by subject ID for use for the repeated assigned sequence of procedure activates. The assignment of each filterline to a CCSF code name will be done by Clinimark and will not be shared with MDT until the device data has been evaluated by CCSF code name to reduce bias.

9.6. Assessment of Safety

Assessing, recording and analyzing safety parameters, including adverse events may occur thought out the study and after each subject enrollment.

9.7. Recording Data

Consent will be confirmed on the case report form (CRF) by a person identified on the delegation of authority as a site monitor to share the device data with the unsigned/unmonitored CRF. The unmonitored/unsigned CRF will be stamped "uncontrolled" by Clinimark before sharing with MDT. Subject's medical historical information will be as supplied by the subject to complete the Health Assessment CRF which will be considered the source in this volunteer out-of-hospital study.

Subject ID CS35 electronic device data recorded on a MDT supplied USB will be transferred to the enterprise MDT Box site after each subject enrollment. MDT has requested that the unsigned/unmonitored CRF stamped by Clinimark as "Uncontrolled" with date be shared with the device data to review the device data. The CRF will be monitored at the end of the study and if a subject did not meet the inclusion/exclusion criteria, subject data will be removed with this protocol deviation. The study device data transferred to the MDT enterprise encrypted and password protected Box site will be considered the source data for data analysis.

9.8. Deviation Handling

Deviations are instance(s) of failure to follow, intentionally or unintentionally, the requirements of the CIP. Intentional deviations are not permitted, except where necessary to protect the life or physical well-being of a subject in an emergency. All deviations must be documented and explained, regardless of the reason for the deviation. Deviations will be documented on the MDT deviation log and escalated to Medtronic within 10 days of identification of the deviation by the site and/or site monitor.

Medtronic is responsible for reviewing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g. additional training and vendor contracts).

If consent was not obtained prior to active enrollment this deviation event will be reported to Medtronic immediately and the IRB as per IRB requirement.

9.9. Subject Withdrawal or Discontinuation

Consented subjects may be withdrawn from the study at any time by the subject or PI with the reason documented on the case report form (CRF). No follow-up post withdrawal is required.

Subject data will be withdrawn from the data pool if insufficient CRF and electronic device data is collected.

Each subject withdrawn before the end of the study will increase enrollment by one but not to exceed total consented at 50 subjects.

10. Risks and Benefits

10.1. Potential Risks

This study will be conducted in accordance with the Declaration of Helsinki and good clinical practice. The study will not commence until the approval has been received from the IRB.

All medical devices used in this clinical study are FDA Cleared products and Medtronic is not aware of any significant problems with these products. In the clinical study, the products will be used in accordance with their labeling/IFU, therefore no risks other than the risks typically associated with routine device use are anticipated.

Risks will be minimized with subject assessment by the Principal Investigator during study procedures. In addition, study risks during the study execution will be minimized by monitoring pulse oximetry in parallel with careful visual assessment of the subject by the study coordinator prior to, during, and after the scripted procedure activates. Should the subject's SpO2 drop below 85% for a duration of 30 seconds, the study activities including the provision of supplemental O_2 will be paused as needed to maintain SpO_2 > 90%. Low flow supplemental O_2 will be supplied to measure the dilution effect on the breath sample provided to the CS35 for measurement not as any treatment. The subject will be advised during the study that he/she may stop the test at any time.

Subjects may withdraw at any time with no consequence.

Procedure Risk for scripted activities:

The potential study activities require minimal physical effort that will repeated for each CO_2 cannula sampling filterline (CCFS) design so risk might be related to boredom more than physical exhaustion. Subjects will be encouraged to take a break as needed to relieve the boredom.

Low flow supplemental oxygen maybe provided at up to 5 lpm to measure CO_2 sample dilution effects as a function of cannula design and/or procedure actives. A subject may refuse supplemental O_2 and/or request to stop the O_2 if uncomfortable and or feeling lightheaded. The reason will be recorded on the CRF.

Insertion and removal of a nasal cannula may cause nasal irritation, discomfort, pain or nasal bleeding. Subject will be visually assessed before and after each cannula change for any adverse events and may be withdrawn if an AE occurs and/or subject request to stop the study.

Medical Device Risk for cleared on label use per IFU includes:

1. Pulse oximetry disposable sensor: Mild to moderate skin irritation or discomfort (redness, itching, rash, pressure) related to the disposable pulse oximetry sensor. The skin will be assessed before and after the application for a potential adverse event. Pulse oximetry will measure the subject's oxygenation saturation during the procedure activities to identify any respiratory compromise adverse event.

2. CO_2 sampling cannula filterlines: Mild to moderate skin irritation or discomfort involved in wearing a nasal cannula with and without an oral scoop/tube above the mouth to collect a gas sample. Designs of the nasal only and oral/nasal cannula interface designs and low pump suction pressure for sampling within the CS35 monitor are means to reduce risk of discomfort.

10.2. Potential Benefits

Volunteer subjects will have no direct benefit for study participation.

The information gained from this study might result in clinical evidence to aid in capnography CO_2 sampling cannula filterline selection for Microstream™ enabled monitors in the clinical setting.

10.3. Risk-Benefit Rationale

Medtronic believes that the potential risks associated with the conduct of this study are minimal and reasonable in relation to the anticipated benefit to provide clinical evidence and guidance on filterline selection.

All the devices used in the study are commercially available and used within their intended use.

11. Adverse Events and Device Deficiencies

Clinimark, an approved clinical vendor with a service agreement for this study, will track all AEs and device deficiencies/failures and report them to MDT as they occur throughout the study.

In this study the following Adverse Events (AE) will be collected:

- All AEs related to the use of the pulse oximeter sensor
- All AEs related to the use of any of the CO_2 sampling filterline
- All AEs related to the procedures of the study
- All Serious Adverse Events

11.1 Definitions/Classifications

Where the definition indicates "device", it refers to any medical device product used in the study. See product description Section 7 for product information.

Table 1. Definition of Adverse Events and Device Deficiency

Term	Abbreviation	Definition
Adverse Event	AE	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether related to the investigational medical device. Note 1: This definition includes events related to the investigational medical device or the comparator. Note 2: This definition includes events related to the procedures involved. Note 3: For users or other persons, this definition is restricted to events related to investigational medical devices.
Adverse Device Effect	ADE	Adverse event related to the use of a medical device. Note 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation or any malfunction of the medical device. Note 2: This definition includes any event resulting from use error or from intentional misuse of the medical device.

Term	Abbreviation	Definition
Serious Adverse Device Effect	SADE	Adverse device effect that has resulted in any of the consequences characteristic of a Serious Adverse Event.
Serious Adverse Event	SAE	An adverse event that a) led to death, b) led to serious deterioration in the health of the subject, that either resulted in 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient or prolonged hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) led to fetal distress, fetal death or a congenital abnormality or birth defect. Note 1: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.
Device Deficiency	DD	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Note 1: Device deficiencies include malfunctions, use errors, and inadequate labelling.

The list of expected Adverse Events that may be associated with the conduct of the study includes:

1. As subjects will be changing their body position throughout the study it is expected that there will be transient decreases in SpO2 below 90%. Should the subject's SpO2 drop below 85%, for a duration of 30 seconds, the study activities including the provision of supplemental O_2 will be paused as needed to maintain $SpO_2 > 90\%$. For this reason, events will only be recorded as an AE if they go unresolved after stopping the study activity.
2. Minor to moderate discomfort at finger sensor site and/or oral/nasal cannula site
3. Itching (pruritis) around or near the location of the sensor and/or cannula site
4. Pain around or near the location for the sensor and/or cannula site
5. Nose bleeds (epistaxis)
6. Dizziness or light headiness

11.2 Reporting of Adverse Events

Adverse Event (AE) information will be collected throughout the study and report to Medtronic on the AE CRF form and recorded on the AE log for each adverse event. It is the responsibility of the investigator to identify the occurrence of adverse events to ensure that the information is accurately documented on the subject AE CRF. The reported AE will be updated with a second AE CRF for the AE closure/reconciliation date if the AE is still open at the time of the initial AE CRF report.

Medtronic medical device deficiencies (DD) will be collect throughout the study and reported to Medtronic on the DD form and recorded on the DD log. Any DDs related to the products not manufactured by MDT would have to be reported to the appropriate manufacturer but will be noted on the DD log to track study device failures in one location.

DDs related to our products will be reported to us in an appropriate amount of time (within 48 hours). Any DDs related to products that we don't make would have to be reported to those manufacturers. Other manufacturer DD will be noted on the subject CRF with the time and description of the failure.

AE documentation will include the following information at a minimum:

- Date of event
- Time of the event
- Description of the event
- Actions taken / treatment
- Assessment of seriousness
- Relatedness to the event (procedure or device)
- Outcome or resolution and date of the resolution

For AEs that require immediate reporting, initial reporting may be done by phone or e-mail. The completed AE CRF must be sent to Medtronic as soon as possible.

Any serious adverse event related to the study procedure or medical device must be report to the sponsor and the IRB per the IRB guidelines as soon as possible, but no later than 10 working days after the investigator learns of the effect.

Emergency sponsor contact information for reporting serious adverse events related to the conduct of the study procedures and serious adverse device effects is the following:

Kathleen H. Niebel RN BSN
Capnography Clinical Project Manager
+1- 978-549-9325
Kathleen.h.niebel@medtronic.com
Or

Lisa Curtis, CCRP
Senior Clinical Research Specialist
Office 303.305.2826 | Mobile 720.216.4670
Lisa.curtis@medtronic.com

The sponsor will ensure timely Adverse Event reporting to meet USA regulatory requirements.

12. Data Review Committee

A data review committee will not be used in this study.

13. Statistical Design and Methods

Medtronic or its designee will conduct statistical analyses of the study data as outlined in the Statistical Analysis Plan (SAP). Any changes in statistical methods will be detailed in the SAP.

The study hypothesis is that the Medtronic (MDT) solution of pairing the Microstream™ FilterLine to the Microstream™ enabled device provides a more reliable gas sample for measurement across many of the patient simulated scripted activities. Performance reliability of each CCSF for sampling breath gas will be measured using the mean and standard deviation for EtCO2, the frequency of false physiological alarms, the frequency of CS35 device notifications, and the frequency of missing CO_2 data (drop-outs) as a function of both the CCSF variable and activity variable by subject and in aggregate.

This hypothesis is based upon the CS35 IFU that recommends that Microstream® $EtCO_2$ consumables (FilterLine) should be used to ensure the monitor functions properly.

The statistical design is a randomized CCSF sequence assignment with each subject serving as their own control within each scripted activity period with the up to 8 CO_2 sampling cannula filterline designs worn in each separate activity period. The randomized sequence by subject is by CCSF code name letters from A – F with the CCSF product assignment to the code name letters done by Clinimark and blinded to MDT

until after the device data has been evaluated. A total of 30 evaluable subject data sets are expected for this study. Based upon a previous study on cannula design investigating both CO_2 sampling and O_2 delivery (Ebert & Novalija, 2015), a sample size of 30 will provide more than 90% power to test a normalized effect size of 5 or more using the Tukey-Kramer multiple comparison test at the 0.05 significance level.

Statistical evaluation of the device data after the first 5 -10 subjects may result in a reduction in the CRF scripted activities for the remaining subjects to remove those activities that would need more than a total of 30 subjects to detect a statistically significant difference in $EtCO_2$ mean as a function of the CCSF for each activity period. This adaptive filtering of the CRF activities purpose is to reduce enrollment time down to activities that may be identified as a potentially statistically significant difference in the sample size and not include those activities that would require an unnecessarily larger sample size for significance.

Descriptive statistics and exploratory data analysis will be used to generate measures of central tendency and to perform data distribution diagnostics. Statistical analysis will entail using the Tukey- Kramer honest significant difference test for multiple mean comparisons. All corresponding P values and confidence intervals for pairwise mean differences will be Tukey corrected as appropriate. Analysis of variance (ANOVA) will be used to compare across multiple groups. Moreover, multivariate regression models will be used to explore the relationship between $EtCO_2$ and supplemental O_2 flow rate after adjusting for factors including cannula type, subject activity and O_2 flow rate.

14. Ethics

14.1 Statement(s) of Compliance

The study will be conducted in accordance with:

- This clinical investigation plan/protocol, good clinical practices and ethical principles that have origins in the Declaration of Helsinki
- International Conference on Harmonization Guidelines on Good Clinical Practice (GCP), local guidelines, and regulatory requirement(s) including 21 CFR 50, 21 CFR 56, 21 CFR 54, and 21 CFR 803.

The study will not commence until IRB approval is received and all required regulatory documents required by the sponsor are complete and up to date including a signed CV, signed financial disclosure, copy of PI medical license. Any additional requirements imposed by the IRB or regulatory authority shall be followed, if appropriate.

Subjects will be compensated 75 USD/hour not to exceed three hours of enrollment for their time as per the informed consent form. Should a subject be withdrawn during the procedures he/she will be compensated up to the closest half hour (37.5 USD/30 minutes). Compensation will be tracked by Clinimark. The 6 previously consented subjects maybe re-consented to perform study activities with the 2 new filterlines (number 5 and 6 on the CCSF list). These 6 subjects will be compensated for their additional time required.

No subject follow-up after discharge from the study will be required. A subject will not be discharged from the study after all study procedures have ended if an adverse event related to the procedures or study devices is not closed as per Section 11. Follow-up on an open AE may include a phone call next day and /or visit to Clinimark by the subject for the PI to assess and recommend medical intervention as needed.

15. Study Administration

15.1. Monitoring

Per the addendum to the master service agreement for this study, Clinimark will monitor the study according to their SOP and provide an electronic copy of the completed signed copies of each enrolled subject CRF and device data file via the Medtronic encrypted and password protected BOX site.

15.2. Data Management

Details of the Data Management are contained in the study specific Data Management Plan.

It is the policy of Clinimark to ensure the confidentiality, integrity, and availability of all Protected Health Information that they create, receive, maintain, or transmit. As such, Medtronic agrees that they will protect against any reasonably anticipated threats or hazards to the security or integrity of such information, and to protect against any reasonably anticipated uses or disclosures of such information that are not permitted or required under the HIPAA Privacy regulation.

Medtronic agrees that all data transmission from Clinimark to Medtronic will be conducted via an encrypted and password protected MDT enterprise Box site. Electronic device data will be compared to subject CRF to verify the match in CCSF code name and time for activity effect on the device measured data. A subject will be withdrawn from the final data pool if there is missing electronic device data for that subject.

15.3. Direct Access to Source Data/Documents

Clinimark and Principal Investigator will permit study-related monitoring, audits, IRB review, and regulatory inspection(s), providing direct access to source data/documents should be included.

Electronic copies of the CS35 device data and both unsigned/uncontrolled and final signed CRFs will be provided to MDT by subject ID via an encrypted and password protected MDT BOX site under the control of MDT clinical engineering. Initial unsigned/stamped uncontrolled CRFs are requested before site monitoring to correlate the activities with the electronic device data for adapting the CRF activity list. The date stamped “uncontrolled” CRF with the subject de-identified device data will not be transferred to MDT until the Clinimark monitor has verified that informed consent has been conducted for that subject and signed the CRF confirmation signature line with date. This data will also be saved in a MDT clinical repository with copies available for data analysis. The electronic de-identified device data will also be returned to MDT on a USB at the end of the study.

15.4. Confidentiality

All records and other information about subjects participating in this study will be treated as confidential. The identity of a subject will never be disclosed in the event study data are published.

Subject confidentiality will be maintained throughout the clinical study in a way that ensures the information can always be tracked back to the source data. For this purpose, a unique subject identification number will be assigned and used to allow identification of all data reported for each subject. Clinimark will maintain the enrollment log with subject information that will not be shared with the sponsor.

Study data may be made available to third parties, e.g. in the case of an audit performed by regulatory authorities, provided the data are treated confidentially and that the subject's privacy is guaranteed.

15.5. Liability

Covidien LP is a wholly owned subsidiary of Medtronic, which as the parent company of such entity maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. Upon request, a copy of the Medtronic "CERTIFICATE OF LIABILITY INSURANCE" will be provided. Clinimark LLC is an approved Medtronic clinical vendor with a current Master Service Agreement.

15.6. CIP Amendments

The investigator may propose any appropriate modification(s) of the Clinical Investigation Plan. Medtronic will review this proposal and decide whether the modification(s) will be implemented.

Medtronic will submit any significant amendment to the Clinical Investigation Plan to documentation control, including a justification for this amendment, to the appropriate regulatory authorities and to the investigators to obtain approval from their IRB, if applicable. Administrative amendments to the Clinical Investigation Plan will be submitted to the IRB and appropriate regulatory authorities for notification, if applicable.

15.7. Record Retention

Investigator records at Clinimark

At a minimum, the following records must be kept by the investigator for two years:

- Clinical Investigation Plan and, if applicable, any amendments
- Medtronic and IRB approved Informed Consent, if applicable
- Regulatory Authority approval or notification, if applicable
- Fully signed clinical investigation agreement and confidentiality agreement (if not included in the clinical investigation agreement)
- Financial disclosures
- Insurance certificates, if applicable
- Completed Delegated Task List and Curriculum Vitae of Primary Investigator and Sub Investigators
- Training documentation of all investigation site personnel
- Copies of the medical device IFUs provided by MDT
- Relevant communications
- Fully executed CRFs and corrections
- Electronic copy of the CS35 de-identified device data on a USB
- Randomization table with CCSF code name key

The investigator must retain the Investigator Site File, subject medical files and eCRF data in accordance with local law and regulations for a minimum period of 2 year (or longer if local laws require) after study completion.

The investigator should take measures to prevent accidental or early destruction of the clinical study related materials.

MDT Sponsor records

At a minimum, the sponsor will keep the following records:

- All essential study documents and correspondence that pertains to the clinical study.
- CIP and, if applicable, any amendments.
- Curriculum vitae of Primary investigators and Sub Investigators Delegated Task. Lists and training records of investigators and site staff.
- IRB approvals/notifications and regulatory approvals/notifications.
- Signed addendums to the Mater Service Agreement for study responsibilities and study execution.
- Medtronic and IRB approved Informed Consent.
- Site selection reports, site initiation reports and monitoring visit reports.
- Copies of the CCSF IFUs provided to the site
- Adverse event reports.
- Financial disclosures.
- Final monitored and approved CRFs.

- Electronic copy of the CS35 device data on an encrypted USB and/or encrypted MDT repository.

15.8. Publication and Use of Information

The results of this clinical study are planned for publication. Publication/Presentation statements will be included in the clinical study agreement between Medtronic and Clinimark.

The study will be registered on www.clinicaltrials.gov before enrollment begins and the informed consent will disclose that information.

The following publication policy will have to be adhered to by all participating investigation sites.

Authorship on any publication(s) resulting from this clinical study will be assigned according to substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content and final approval of the version to be published. Names of the participating investigators will appear in the Acknowledgment of the paper.

Medtronic as the owner of the data can use the data and/or any results derived from the data or publications based on that data for marketing purposes, further research and development of devices or educational use. The use of the study data information may support MDT clinical recommendations to customers on filterline selection for Microstream™ enabled monitors.

The study sponsor will collect data in such way that no subject can be identified, and monitor study records.

Participating subjects will not be identified by name in any published reports about the clinical study.

15.9. Suspension or Early Termination

Early termination results when the study is closed prior to the end of the study. A study suspension is a temporary postponement of the study activities related to enrollment. Both are possible for the study.

If the study is terminated or suspended, no additional enrollment will be allowed unless otherwise informed by the sponsor. The current subjects will be followed according to the protocol.

Medtronic or Regulatory Authority may decide to suspend or prematurely terminate the clinical study. If the clinical study is terminated prematurely or suspended, Medtronic shall promptly inform the clinical

investigators of the termination or suspension and the reason(s) for this. The investigator shall then promptly inform the reviewing IRB and the study subjects or their legal representative.

Medtronic, IRB or Regulatory Authority may decide to suspend or prematurely terminate an investigation site (e.g. in case of expiring approval of the reviewing IRB, non-compliance to the Clinical Investigation Plan, or lack of enrollment). If an investigation site is suspended or prematurely terminated, Medtronic shall promptly inform the investigator(s) of the termination or suspension and the reason(s) for this. The investigator shall then promptly inform the reviewing IRB, if required, the study subjects or their legal representative.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definite outcomes, investigators must assess whether to continue, modify or immediately stop the clinical study in the respective investigation site and immediately inform the sponsor and IRB, if applicable.

If the investigator (or IRB) terminates or suspends the investigation without prior agreement of the sponsor, the investigator will promptly inform the sponsor, the institution (if required) and the IRB, and provide a detailed written explanation of the termination or suspension. The sponsor will inform the regulatory authorities (if required).

In case of early termination of the study, all study subjects should be followed until the resolution of any pending adverse event(s).

Medtronic reserves the right to discontinue the study at any time for administrative or other reasons. Written notice of study termination will be submitted to the investigator in advance of such termination. Termination of a specific site can occur because of, but not limited to, inadequate device data collection, low subject enrollment, or non-compliance with the protocol or other research requirements.

In case of close out, the investigators will be notified and notification/report to Medtronic and Regulatory Authority will be done, if required.

16. References

1. Ebert, T. J., & Novaliia, J. M. (2015, February). The Effectivieness of Oxygen Delivery and Reliability of Carbon Dioxide Waveforms: A Crossover Comparison of 4 Nasal Cannula. *Anesthesia & Analgesia, 120*(2), 342-248.

2. Marshall, S. G., Henry, N. R., & Russian, C. (2016, April). Right Versus Left Prong Nasl Annula FLow Delivery and the Effects of Nasal Cycling on INspired FiO2 in an Adult Anatomical Model. *Respiratory Care, 61*(4), 397-404.

17. Version History

Version	Summary of Changes	Author(s)/Title
1.0	Not Applicable, New Document	Kathleen H. Niebel RN BSN
2.0	Rename the CCSF list to be numbers since the randomization table is alphabetic to maintain blind for analysis, replaced two CCSF filterlines, clarified an SpO2 AE, adjusted the sample size based upon volume of data collected (7200 data points per activity), added request to reconsent six to test just the two CCSF devices replaced and clarified conditions for transfer of data to MDT.	Kathleen H. Niebel RN BSN