Full Protocol Title: A NEW AND INNOVATIVE METHOD FOR CO_2 REMOVAL IN ANESTHESIA CIRCUITS: REPLACING CHEMICAL GRANULATE ABSORBERS

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Roles and Responsibilities:
Principal Investigator: Dr. Orlando Hung, MD, FRCPC
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Research Coordinator: Vera Lloyd
Sub-Investigator(s): As per Appendix B

TABLE OF CONTENTS

SYNOPSIS

a. Study Title
A NEW AND INNOVATIVE METHOD FOR CO_2 REMOVAL IN ANESTHESIA CIRCUITS: REPLACING CHEMICAL GRANULATE ABSORBERS

b. Objectives
To demonstrate that memsorb can maintain safe levels of CO_2, measured at the end of expiration throughout the duration of anesthesia in patients of varying weight and ventilation requirements during different surgical procedures.

c. Design and Outcomes
This is an investigational study comparing two methods of CO_2 removal in anesthesia – the first being traditional chemical granulate, and the second being memsorb™ a CO_2 filtration system that relies on medical membranes and flush gas to remove CO_2 from the patient rebreathing system. Participants will be assigned to groups based on their willingness to participate and group capacity at that time. Patients will be consented to the device intervention or control group. The trial will evaluate the equivalence of the two CO_2 removal methods. Standard electronic data collection will occur during the induction and maintenance of general anesthesia throughout the procedure. Data will be pulled from the anesthesia database.

d. Interventions and Duration
Intervention participants will consent to the use of the memsorb filter for the length of time required to perform their elective surgery procedure.

e. Sample Size and Population
Approximately three hundred participants from the general population scheduled to undergo elective surgery will be recruited.

Principal Investigator Approval Statement

I have read this protocol and agree to conduct this clinical trial as outlined herein. I will ensure that all sub-investigators and other study staff members understand all aspects of this protocol. I will adhere to the Declaration of Helsinki and its amendments, the International Conference on Harmonization (ICH) principles of Good Clinical Practice (GCP; including archiving of essential study documents) and all applicable regulations and guidelines of the country in which the study is conducted.

Principal Investigator:

Printed Name: Dr. Orlando Hung

Signature: _____

Date: _____

A NEW AND INNOVATIVE METHOD FOR CO2 REMOVAL IN ANESTHESIA CIRCUITS: REPLACING CHEMICAL GRANULATE ABSORBERS

Protocol Revised: 2021-12-20

1. STUDY OBJECTIVES AND OUTCOMES

The purpose of the proposed research trial is to validate earlier bench, animal results and human results in a larger patient population. Therefore, the study is designed to directly compare the memsorb filter device with currently used chemical granulate absorbers used at Nova Scotia Health in 300 elective surgeries. The primary objective of this analysis will demonstrate that memsorb can maintain safe levels of CO_2, measured at the end of expiration throughout the duration of anesthesia in patients of varying weight and ventilation requirements during different surgical procedures.

1.1. Objectives

1.2. Primary Objectives

The primary objective of this trial is to compare the performance of memsorb™ relative to the chemical granulate absorbers currently used at Nova Scotia Health and most other hospitals in Canada. memsorb™ removes CO_2 from the patient circuit using hollow fiber membrane filtration. Exhaled CO_2 diffuses through the hollow fibre membrane due to a partial pressure gradient. The CO_2 is then removed from memsorb™ via a flush gas which is comprised of medical oxygen and air.

Our primary outcome measure will be a simple YES (1) or NO (0), stating if the expiratory ($EtCO_2$) levels stayed in the clinically desired range of (4.1-5.6) % CO_2 with both manual and electronic flush gas blenders. In addition, both groups will be compared using an ANCOVA, where secondary measures will be used as variables for the ANCOVA to increase power.

$EtCO_2$ is an accepted surrogate measure to assess the concentration of CO_2 in the blood ($paCO_2$) and therefore the pH. This is common practice for anesthesiologists worldwide, avoiding the need for repeated invasive blood gas analysis. The $EtCO_2$ is therefore the most important patient ventilation parameter besides the oxygen saturation of hemoglobin SaO_2. See “Data Analyses” (Section 9 below) for a statistical summary.

Secondary measures that will have no direct clinical impact will also be collected. These measures include length of surgery, method of ventilation, an export of the content of the ‘notes field’ from Innovian, inhaled and exhaled fraction of anesthetic agent, vapour use (where available), fraction of inspired and expired oxygen (FiO_2, FeO_2), fraction of inspired Carbon Dioxide ($FiCO_2$), arterial blood gas analysis results (pH and $paCO_2$ where available), patient temperature, relaxation status (train of four) during surgery (where available), ventilation frequency, minute volume (MV), tidal volume (TV), ventilation pressures (i.e. peak, mean, peep and plat pressure), fresh gas flow, and compliance (ml Tidal Volume/ cmH_2O ventilation pressure), along with physiological parameters such as heart rate, blood pressure (where available), SaO_2, SpO_2, and biometric data such as patient weight and height, age, medication, history of lung disease will provide metrics to demonstrate other ventilator parameters remain in the target range of (4.1-5.6) % CO_2, and will be collected through the anesthesia and nursing databases. Additionally, relative humidity and temperature of the circuit will be measured throughout surgery via a dedicated port in the inhalation and exhalation leg of the anesthesia re-breathing circuit. Relative humidity and temperature will also be measured in a defined volume ~[50mL] of the exhaled gas coming from the participant on the patient side of the HME filter

using a sterile sampling line. In a sample of patients, a measurement of the pH at various points within the re-breathing circuit, using litmus paper, will be taken following the extubation of the participant.

Secondary Objective
The secondary objective of this study is to examine the use of the memsorb filter device by anesthesiologists whose standard-of-care includes the use of low fresh gas flows.

Tertiary Objective
This study will also evaluate the useful life of up to 50 chemical CO_2 absorbers by tracking the number of hours they are used before being discarded. This portion of the study will not require any participant data collection.

New objective
Two different methods of flush gas supply will be compared – the standard manual flush gas blender that has been used to date [Manufacturer: Precision Medical HC License 71950] and electronic flush gas blender [HC ITA# to be determined].

The electronic flush gas blender will be evaluated to demonstrate it can electronically adjust the flush gas composition supplied to memsorb™ to match the composition of the machine-side gas set by the anesthesiologist (Target FiO_2). This will be evaluated using standard ventilation parameters collected by the Innovian® system (e.g., machine-set target concentration of FiO_2, and patient FiO_2).

BACKGROUND

In recent years anesthesia and surgery have been shown to incite a syndrome known as Post Operative Cognitive Decline (POCD) (Bryson & Wyand 2006). The syndrome is particularly common in elderly patients and patients undergoing procedures involving the cardiopulmonary bypass (CPB) (Silverstein et al. 2007).
Half of all the surgical procedures performed in 1999 were performed on elderly patients 65 years or older, reflecting 12% of the current population. This number is increasing (Etzioni et al. 2003). Patients with POCD often exhibit impaired cognitive functioning in their thinking, perception and memory, and they have a more than fivefold increase in their mortality rate for the 12 months after surgery and anesthesia (Monk et al. 2005; Lewis 2007). The type of surgery performed and the age of the patient both affect the risk of developing POCD, with very young and elderly patients being at particularly high risk (Rasmussen 2006). The average incidence rate of POCD ranges up to 25% (Bryson & Wyand 2006) where the highest incidence is reported for cardiac surgery at up to 70% (Silverstein et al. 2007).
Enough concern has been raised in relevant medical circles to warrant the attention of the Anesthesia Patient Safety Foundation (APSF) of America (since 2004). More recently a New York Times article highlighted the FDA's Smart Tots program in collaboration with the International Anesthesia Research Society (IARS) which explores the side effects of vapor

anesthesia on the cognitive development especially in children, further illustrating this issue's recognition in the public consciousness.
In addition, the fastest growing segment of the population is those 65 years of age and older. According to the US Census Bureau this age segment will grow by 53.2% in comparison to the overall population with a predicted growth of 17% from 2010 to 2020, making POCD a growing issue that fewer people can pay for (see Figure 1). POCD is likely to impair quality of life and constitutes a large burden on society when elderly patients prematurely lose their independence. (Gao et al. 2005) Research findings suggest that even a small improvement in 1-year cognitive outcome could mean thousands of lives saved each year. (Monk et al. 2004).

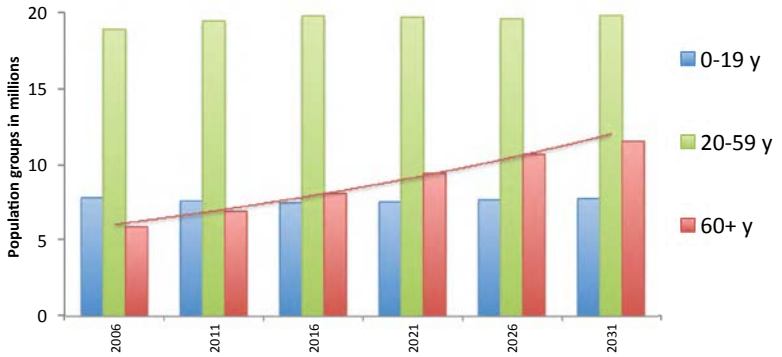


Figure 1: Data from Statistics Canada, CANSIM, table 052-0004 and Cat. no. 91-520-X showing the population groups in millions for the year 2006–2031

Challenges in Modern Anesthesia

Modern anesthesia systems pose a dilemma. To minimize the loss of expensive anesthetic vapor, modern systems aim to be as closed as possible. In an ideal world, a completely closed circuit would only need replacement of the amount of oxygen and vapor metabolized by the patient (<5%) and extraction of the metabolic end-product CO_2. To extract the CO_2 from the anesthetic circuit, carbon dioxide scrubbers have to be employed (see Figure 2)
Scientists have confirmed that existing CO_2 absorbers produce by-products which are toxic to patients (Morio 1992). These by-products result from the degradation of the anesthetic drug, which occurs when it reacts with the chemical granulate, supposed to only react with CO_2. The resulting neuro and nephro-toxic compounds build up in the circuit where patients are exposed to them over the entire duration of the anesthesia. Over the past several years, these degradation compounds are well described and known to be nephro- (Stabernack et al. 2003) and neuro-toxic (Konat et al. 2003). It is discussed that these toxic compounds contribute to organ damage after anesthesia and surgery and are possibly contributing to the brain damage after surgery that is also known as Post-Operative Cognitive Decline (POCD). The major known degradation products of vapourized Sevoflurane are well known as Compound A-E for decades and described in textbooks and scientific literature (Stabernack et al. 2003). Compound A and

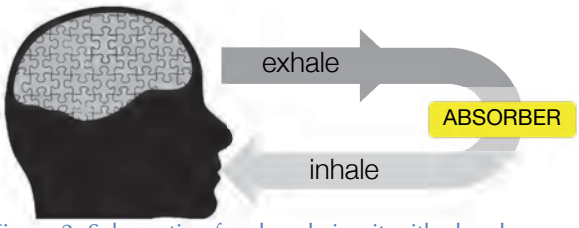


Figure 2: Schematic of a closed circuit with absorber

its toxicity to the kidney and brain cells are described best in literature. Brain cells in a culture die after being exposed to Compound A (Konat et al. 2003).
These findings have resulted in the requirement for a minimum fresh gas flow into the anesthetic circuit, replacing up to two thirds of the volume in the circuit each minute to dilute these toxic compounds. While a CO_2 absorber makes closed circuit per se possible, current absorbers stay in the way of safely achieving a fully closed circuit. Reducing the fresh gas flow linearly reduces the amount of vapour used (Ekbom et al. 2007). For example, reducing the fresh gas flow from 3l/min to 1.5l/min reduces the required anesthetic drug use from (0.16±0.05)ml/min to (0.07±0.03)ml/min (Doolke 2001).

Current absorbers also form corrosive (alkalotic) dust that may accumulate in the ventilation circuit (see Figure 3). Even the best filters available (combined bacterial/viral filters separating the patient from the anesthetic circuit) allow dust particles smaller than 20 nm to get pass the filter and enter the patient's lungs. Larger dust particles can accumulate on the filter's surface, come into contact with water sitting on the filter and therefore potentially pass the filter in solution. If this dust or solution is allowed to contact tissue for any length of time, a chemical burn will occur and can potentially lead to life threatening conditions such as laryngospasm, bronchospasm or pneumonia (Sodasorb 1993). The dust also accumulates in the circuit and can lead to fatal mechanical failures like blocked valves (Kummar et al. 2009).

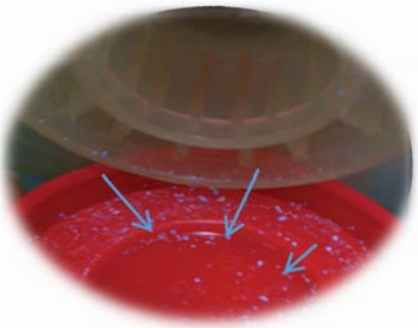


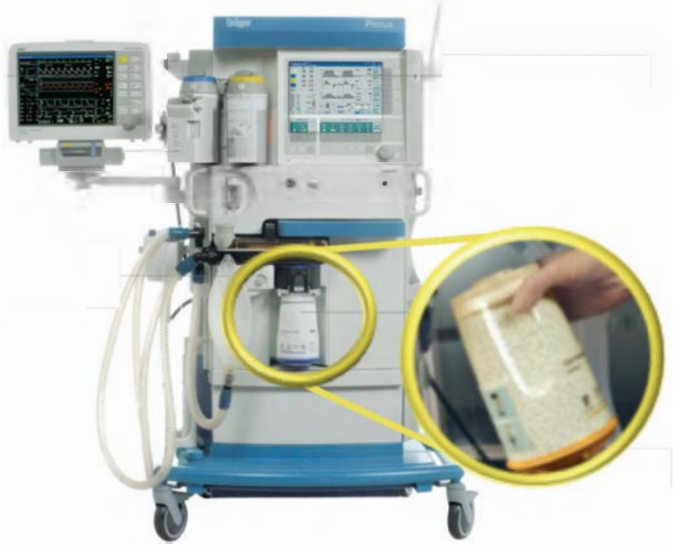
Figure 3: Alkalotic dust in the cap of a newly unpacked absorber

Description of the Device: memsorb

memsorb is a patented innovative carbon dioxide (CO_2) filter that aims to remove CO_2 from anesthetic circuits as effectively as current chemical absorbers. memsorb is a class II device approved for sale by Health Canada (license no. 104717). This device is unique in that aspect, instead of chemically binding the CO_2 as state of the art absorbers, it separates the CO_2 from the residual gas components including the anesthetic drug within the circuit without any chemical granulate that could cause degradation of vapors. Existing anesthetic machines use chemical granulate loosely packed in a container to absorb exhaled CO_2 (see Figure 4). In the process, not only the CO_2, but also the anesthetic drug reacts with the chemical granulate and creates the known compounds A-E. It also creates other toxic substances such as carbon monoxide, formaldehyde, and methane to name just a few.

Our innovative alternative to the classic absorber, memsorb, uses an alternate process to remove the CO_2. Instead of absorbing (chemically binding) the CO_2, memsorb separates the CO_2 from the gas mixture using membrane technology and removes the CO_2 via a flush gas as evaluated previously.

Figure 4: Draeger anesthesia machine with state-of-the-art chemical absorber



The flush gas is comprised of medical oxygen and air at a concentration equal to the machine-side target fraction of O_2. To date, the flush gas has been blended and administered via a manual blender (Precision Medical, HC License #71950). An electronic blender (HC ITA# 335727) will be evaluated to automatically adjust the flush gas to match the machine-side target fraction of FiO_2.

The device uses membrane technology, which has been proven effective and safe in other medical applications like dialysis and blood oxygenation for decades.
The test device is capable of being used with any anesthesia machine/ system in the world today, as it is similar in shape, size, and interface to existing absorber cartridges, provides the same performance and therefore does not require additional training or change in clinical practice. (Note: installation is identical to current absorber cartridges as explained in L-SOP-14001 provided in Appendix A)

1.3. Rationale

CO_2 removal is a mandatory part of modern anesthesia systems. Current chemical absorbers pose problems as the chemical granulate reacts not only with the CO_2 but also the anesthetic

drugs, producing organ toxic substances. The proposed CO_2 filter, memsorb, provides a solution to the problem of organ-toxin production in anesthetic circuits.
memsorb can be easily integrated into any anesthesia circuit and can effectively remove CO_2 without reacting with anesthetic drugs, thus eliminating organ-toxic by-products.
memsorb uses advanced membrane technology to separate gas flows within the circuit, separating the expensive anesthetic vapors from the CO_2 (the main by-product of metabolism). Anesthetic vapors thus remain in the closed loop circuit, while CO_2 is separated and exhausted to the atmosphere, rather than being absorbed through a chemical reaction.

1.4. Supporting Data

Previous Work To Date

The performance of memsorb has been studied in large animal (pig) studies led by Dr. Michael Schmidt using standard human patient equipment and pilot study in humans led by Dr. Orlando Hung.
The human study in 2014 compared memsorb to the market leader in CO_2 absorption (Draeger) in a human clinical trial with 20 subjects. This pilot-study showed that memsorb is as effective and safe as the market leader. There were no adverse events reported.

The pig studies have demonstrated that this device is highly effective in maintaining expiratory CO_2 levels necessary to maintain a stable pH in the animal. The pig model organism provides highly similar anatomical, physiological, and genetic landscapes to those observed in humans. In addition, chemical granulate CO_2 absorbers that are the current standard in human anesthesia perform in an identical fashion when used in pigs.
As a pre-clinical model, a pig model was chosen since their pulmonary physiology allows for the use of unmodified, full size, state-of-the-art equipment used in humans.

After ethics approval by the local animal care committee, pigs received a mask induction using Sevoflurane. Once asleep, they were intubated and ventilated by an anesthesia machine (Tangens 2C, EKU, Germany).
While the anesthesia machine supplies on-board state-of-the-art monitoring of the ventilation parameters, a patient monitor (Datex Ohmeda, Sweden) was connected to collect additional ventilation data. Figure 5 shows the pressure-volume relationship (compliance) and the flow-volume relationship of the system. Furthermore, the peak (Ppeak) plateau (Pplat) and PEEP pressures as well as the inspired (TVinsp) and expired (TVexp) volumes are displayed.

Figure 5: Sample spirometry data from Datex Ohmeda patient monitor. (left) flow-volume relationship of the system, (right) compliance (pressure-volume relationship). Furthermore, the peak (Ppeak) plateau (Pplat) and PEEP pressures as well as the inspired (TVinsp) and expired (TVexp) volumes are displayed.

When replacing the traditional, chemical granulate based absorber with the test device memsorb, compliance[1], flows and pressures were observed using the patient monitor data (Figure 5). None of the parameters on the patient monitor regarding compliance, flows and pressures changed when switching to memsorb.

End tidal CO_2 ($EtCO_2$) is a clinically accepted surrogate measure for the CO_2 concentration ($paCO_2$) in the patient's blood. Keeping the $paCO_2$ in a range of (40±4) mmHg is important to keep the directly dependent pH[2] in the patient's blood in a healthy range. The gradient between the $paCO_2$ and the $EtCO_2$ is typically in the range of (1-5) mmHg (Corbo et al. 2005) resulting in a safe range for the $EtCO_2$ of (31-43) mmHg equivalent to (4.1-5.6) % at normobaric pressure[3]. All standard parameters of ventilation were applied for testing memsorb (see Table 1).

Table 1: Ventilation parameters used

Frequency [breath × min^{-1}]	**Tidal Volume** [ml × breath^{-1}]	**Minute Volume** [liter × min^{-1}]
12	600	7.2

There were no obvious changes observed in flow patterns, circuit compliance, pressures or volumes delivered under usage of memsorb. There was no difference in operating memsorb in comparison to the state-of-the-art absorber from the anesthesiologist's perspective.

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[1] Flow per pressure unit

[2] $pH = 6.1 + \log_{10}\left(\frac{[HCO_3^-]}{0.03 \times PaCO_2}\right) pH = 6.1 + \log_{10}\left(\frac{[HCO_3^-]}{0.03 \times PaCO_2}\right)$

[3] 1 atm = 760 mmHg. (40/760) = 5.3%

The primary outcome measure $EtCO_2$ was continuously in the target range of (4.1-5.6) % CO_2 using memsorb (see Table 2) and kept stable.

Table 2: In vivo test data with different fresh gas mixtures and flows resulting in $EtCO_2$ values reliably in the physiologically desirable range of (4.1-5.6) % CO_2.

Fresh Gas [litre × min^{-1}]	**Fresh Gas** [%O_2, %Air]	**$EtCO_2$** [%] MEAN	±STDEV
2	100, 0	5.32	0.15
4	100, 0	5.20	0.05
2	50, 50	5.28	0.15
4	50, 50	5.32	0.04

All data is unpublished research data from the Michael Schmidt Research Group. Animal Care approval and Health Canada drug exemption were obtained before conducting this study. Based on these results, we expect that memsorb will perform safely and effectively in human subjects.

2. STUDY DESIGN

This is an investigational study comparing $EtCO_2$ levels in patients using either a new CO_2 filter memsorb, or the standard chemical granulate absorber. Flush gas through memsorb™ will be provided via a manual Health Canada–approved air-oxygen blender, or an electronic blender under Health Canada Investigational Testing Authorization. Participants will be assigned to groups based on their willingness to participate and study capacity. Patients who do not consent to using the new device may be given the option to participate as control patients.
The current trial will evaluate the equivalence of two CO_2 removal methods. Standard electronic data collection will occur during the induction and maintenance of general anesthesia throughout the procedure. Data will be pulled from the anesthesia and nursing databases (Draeger Innovian and McKesson Horizon Surgical Manager respectively.

3. SELECTION AND ENROLLMENT OF PARTICIPANTS

3.1. Study Setting and Sample Size

Approximately three hundred patients undergoing general anesthesia for an elective surgical procedure will be recruited from either the Queen Elizabeth II Health Sciences Center (QEII HSC), Halifax, Nova Scotia or the Dartmouth General Hospital (DGH), Dartmouth, Nova Scotia. See *Standard Operating Procedure for Obtaining informed consent and enrolment in memsorb study trial* and attached recruitment flow chart.

Participants will receive the same treatment / anesthesia per the standard of care at Nova Scotia Health. There is variation from the standard of care in the interventional group by the use of a Health Canada–approved device (memsorb). The anesthesia procedure will be performed according to the standards of the attending anesthesiologist. If a participant is willing to be included in the interventional group, the standard chemical granulate absorber will be replaced with a memsorb filter. If a participant is not interested to be included in the interventional group, the regular chemical granulate absorber will be used for the procedure.

Due to the technical nature of this trial and our goal of maintaining the highest standard of safety for the patient, the anesthesiologist will not be blinded to the absorber/filter type (chemical absorber or memsorb filter) being used during surgery. Additionally, since we are using objective measures, i.e., $EtCO_2$, the anesthesiologist will not need to be blinded to the group.

3.2. Eligibility Criteria

3.2.1. Inclusion Criteria

- American Society of Anesthesiologists Physical Status Class I, II, III (low-medium risk patient)
- English-speaking patients

3.2.2. Exclusion Criteria

- Self-reported as pregnant
- American Society of Anesthesiologists Physical Status Class IV (high risk patient)
- Patients scheduled for emergency surgery
- Documented respiratory disease, such as COPD and severe asthma
- Documented elevated pressure in the brain (intra cranial pressure, ICP)

3.3. Study Enrollment Procedures

3.3.1. Methods for identifying and recruiting candidates for the trial

Following the Informed consent and enrolment procedure for memsorb clinical study and attached recruitment flow chart, approximately three hundred participants,110 in the control group and 190 in the intervention group, will be recruited on the day of surgery. During registration with the front desk, the patients will be asked by staff if they are interested in being approached for a research study, and if they are willing to sign the “Access to Personal Health Information” form for screening purposes. Patients will be identified by a member of the research team using the screening parameters and will be offered the opportunity to participate in this research study and upon expression of interest to participate, will be walked through the informed consent process. The participants will be informed that the final decision about enrollment will be based on the anesthesiologists’ assessment for fit during the pre-op assessment. The anesthesiologist and research coordinator will be on hand to answer any questions the patient may have. Two hundred patients will be recruited for the memsorb group, using the “Informed Consent Form, Clinical Trial – Device”, and one hundred patients will be recruited for the control group, using the “Informed Consent Form, Clinical Trial – Control”.

During surgery, any adverse events during the use of memsorb will be reported in the Patient Safety Reporting System as mandated by NS HEALTH, the REB, and Health Canada.

3.3.2. Consent procedures

Refers to the Informed consent and enrolment procedure for memsorb clinical study.

3.4. Randomization Procedures

Not Applicable

3.4.1. Sequence Generation

Not Applicable

3.4.2. Concealment Mechanism

Not Applicable

3.5. Blinding

Not Applicable

STUDY INTERVENTIONS

3.6. Interventions, Administration and Duration

Intervention participants will be screened for a study operating room in which their surgery will be performed, whether the anesthesiologist scheduled for that room will be trained on the use of the memsorb filter and delegated to this study, and for a procedure expected to be performed under general anesthesia. Enrolment will be conducted per the memsorb Device Installation and Basic Use Training Procedure. Intervention participants who consent will use the memsorb filter for the length of time required to have their elective surgery procedure performed. The anesthesia procedure will be performed according to the standards of the attending anesthesiologist.

3.7. Handling of Study Interventions

Patients in the interventional group will be recruited from Nova Scotia Health sites noted in section 4.1 undergoing general anesthesia for an elective surgical procedure and will receive the memsorb device in lieu of the standard Draegersorb device.

3.8. Concomitant Interventions

Not Applicable.

3.8.1. Required Interventions

Not Applicable.

3.8.2. Prohibited Interventions

Not Applicable.

3.8.3. Precautionary Interventions

Not Applicable.

3.9. Adherence Assessment

3.10. Not applicable.

4. CLINICAL AND LABORATORY EVALUATIONS

4.1. Schedule of Evaluations

Not applicable as the length of this study for participants is for as long as the general anesthesia procedure lasts. The total length of participation will depend on the length of surgery. There are no pre or post clinical evaluations.

4.2. Timing of Evaluations

Not Applicable

4.2.1. Pre-Intervention Evaluations

Not Applicable

4.2.1.1. Screening

As per the Investigator Information Sheet

4.2.1.2. Baseline Evaluations

Determine if the potential participant satisfies the eligibility requirements as per the memsorb study inclusion / exclusion criteria

4.2.1.3. Intervention Assignment and/or Initiation

After it is determined that the participant satisfies the memsorb study criteria and after informed consent for either the interventional or control group has been obtained an enrollment number is assigned. The anesthesiologist performs a final assessment for fitness for the study for participants consented for the interventional group. Ability to assign patients to either group, together with interest by the patient to participate generates a non-biased assignment of patients to either group, which could be considered random.

4.2.2. On-Intervention Evaluations

Since the anesthesia procedure will be performed according to the standards of the attending anesthesiologist no additional evaluations outside the standard of care will be performed.

4.2.3. Intervention Discontinuation Evaluations

If during surgery, the memsorb filter fails, the anesthesiologist will swap the experimental device for the standard chemical-based CO_2 absorber, or, in the event there is not a standard device available, the circuit will be opened to vent CO_2 out the stack. There will not be any additional evaluations outside the standard of care.

4.2.4. Post-intervention Follow-up Evaluation

No further follow-up will be required as we are only using intra-operative data.

4.2.5. Final Evaluations

Not Applicable

4.2.6. Post-Study Requirements

Not Applicable

4.2.7. Pregnancy (Optional)

Not Applicable

4.3. Definitions

4.3.1. Informed Consent

A participant's agreement to participation in a clinical study after being properly advised of the relevant medical facts and the risks involved.

4.3.2. Control Participant

Surgery is conducted using the standard CO_2 absorber, and only data is collected. There is no difference in how the anesthesiologist will manage general anesthesia during surgery. There will not be any additional treatments.

5. ADVERSE EVENTS

During surgery, any adverse events during the use of memsorb will be reported in the Patient Safety Reporting System as mandated by NS HEALTH, the REB and Health Canada.

Adverse advents will be reviewed and if determined to be related to the memsorb filter, be reported to the REB per their requirements. All serious unexpected adverse reactions will be reported to Health Canada per Health Canada's Mandatory Problem Reporting guidelines (from Health Canada's Medical Device Regulations) and the sponsor.

6. CRITERIA FOR DISCONTINUATION

6.1. Study Withdrawal Procedures

Participants may withdraw at any time and their information will not be used in the data analysis.

6.2. Termination or Suspension of the Study

The study sponsor, the Nova Scotia Health Research Ethics Board, Health Canada, and the principal investigator have the right to stop patient recruitment or cancel the study at any time.

7. STATISTICAL CONSIDERATIONS

7.1. General Design Issues

This study aims to compare the ability of current chemical CO_2 absorbers and memsorb to maintain safe $EtCO_2$ levels in a variety of patients. In order to increase power, additional patient and ventilation parameters will be investigated for their fit as co-variables in the main analysis. In general, they will also allow the detailed description of the patient population in each group and may provide the ability to subdivide the patient populations into homogenous patient populations if not given already.

The memsorb filter device has a feature which supports using fresh gas flows less than 1Lpm. Current CO_2 absorbers (control) do not recommend fresh gas flows lower than 1 Lpm. Since low fresh gas flow equivalence of the two devices cannot be compared, a subset of participant data using the memsorb device only, will be collected using anesthesiologists whose standard-of-care includes the use low fresh gas flows.

We propose that 300 participants are recruited to the study overall.

190 intervention participants be recruited:

- 130 procedures requiring general anesthesia be performed using the memsorb filter device
- 60 procedures requiring general anesthesia be performed using the memsorb filter device and anesthesiologists whose standard-of-care includes the use of low fresh gas flows.
    - From this cohort, 40 participants will be assigned memsorb™ with the electronic flush gas blender

Metrics from these procedures will be compared to that derived from 110 procedures using the current standard of care (controls), which is a chemical granulate based absorber.

7.2. Outcomes

7.2.1. Primary outcome

The experimental design will include the independent variable of CO_2 removal, by comparing the traditional chemical granulate absorber device, (control) to the memsorb CO_2 membrane filter device (interventional) to determine if they are maintaining the CO_2 at safe levels.

Ventilation and patient parameters, potentially influencing the primary outcome, will be collected and analyzed for their fit to be used as covariates for the primary outcome analysis in order to aim for increased power, sensitivity and potentially the ability to describe homogenous subgroups in case the patient population is not normally distributed in regards to key primary or secondary parameters.

7.2.2. Secondary outcomes

The study will collect data from anesthesiologists' whose standard-of-care includes the use of low fresh gas flows when using the memsorb filter device.

7.2.3 Tertiary outcomes

This study will track the number of hours each chemical CO_2 absorber is in use (from initial installation through to discarding), to establish the average lifespan of traditional CO_2 absorbers. The FGF at which each CO_2 absorber is used will also be collected in order to establish an exhaustion curve to determine the average lifespan in view of fresh gas flows.

7.2.4 Quaternary outcomes

This outcome will evaluate the ability of an electronic flush gas blender to provide a flush-gas through memsorb™ that matches the concentration of the machine-set target fraction of O_2. The flush gas should be the same concentration as the machine side gas to limit partial pressure differences in O_2, which could cause O_2 to transfer across the membrane.

To determine the flush gas concentration is not statistically different from the machine-side gas concentration, two measures will be extracted from the Innovian® system; machine-set target fraction of O_2, and patient side FiO_2. A statistically insignificant difference between the two values indicates the flush gas concentration was successfully matched to the machine-side concentration. The analysis will be performed using standard statistical methodologies.

7.3. Sample Size and Accrual

Due to a lack of reported effect size data related to this technology, a formal power analysis cannot be provided. 200 patients is considered "typical" for a device safety study with HC and the FDA. This is a clinical trial for a Class II medical device. In comparison, drug clinical trials at the same stage of development (Phase II Clinical Trials) enroll between 100 and 300 participants. Based on this it was determined that a total of 300 participants would be recruited for this clinical trial. A direct comparison of 110 hundred participants in the control group and 130 participants in the intervention group will be performed. Also, data from approximately 60 additional participants consented to the intervention group only, will be collected to evaluate standard-of-care use of low fresh gas flows.

7.4. Data Analyses

The primary variable $EtCO_2$ is given as repeated measures and will therefore be analyzed using an ANCOVA. ANCOVA in this case provides the additional benefit over an ANOVA, that secondary parameters can be used as covariates in order to potentially increase power and sensitivity. Secondary parameters may also be used, to subdivide the group data into more homogenous subgroups for representative purposes in addition to the ANCOVA.

The data from the 50 participants where anesthesiologists' standard-of-care while using the memsorb device includes using low fresh gas flows will help establish and provide supporting documentation for an initial range of fresh gas flows suitable for use with the memsorb device.

8. DATA COLLECTION AND QUALITY ASSURANCE

8.1. Data Collection

Innovian and HMS
Primary and secondary parameters are exported from the Anesthesia Innovian and nursing perioperative documentation system (Horizon Surgical Manager).

Manual data collection
Useful lifespan of chemical CO_2 absorbers is recorded manually from study staff (medical students) whenever cartridges are replaced in the OR. The fresh gas flow rates at which the CO_2 absorbers are used will be recorded during each procedure to establish an exhaustion curve. No participant data will be collected during this portion of the study.

8.2. Study Records

8.2.1. Data Management

The Data export from the Innovian and HMS databases is managed by the quality improvement office of the Department of Anesthesia. Data is de-identified by the Research Coordinator and only the de-identified data becomes part of the binder accessible by all study staff and is provided to the study sponsor.

All data transfers are protected by TLS and is encrypted using 256-bit AES encryption.

Data will be deleted from all storage device of the study group and the sponsor after 25 years and all paper records will be destroyed. Only data required by scientific papers and regulatory agencies for documentation purposes will be kept beyond that point.

8.3. Quality Assurance

Not applicable.

9. SAFETY MONITORING

Anesthesia has been performed with semi-open (without any CO_2 absorber) systems for decades, safely. This proves that even in the unexpected case of a malfunction of a memsorb device, anesthesia can be performed safely without ***any*** CO_2 absorption in the circuit using a higher level of fresh gas flow. This can be achieved by opening up the circuit and continuously venting fresh gas. Because of this, there is no additional risk to the patient if the test device, or standard chemical granulate absorber, does not perform as expected. A failure of memsorb is equivalent to the regular exhaustion of current chemical absorbers and therefore reacting to such incident is standard practice.

10. ETHICAL CONSIDERATIONS RELATING TO THE TRIAL

10.1. Research Ethics Board (REB) Review and Informed Consent

i. There are no direct benefits to participating in this trial, besides enlarging the body of knowledge in the field.

ii. Informed consent is obtained as per the Standard Operating Procedure for Obtaining informed consent and enrolment in memsorb study trial.

iii. Study bias is minimized through the assignment of suitable participants. NS HEALTH assigns potential participants to a specific OR room, with a specific anesthesiologist. The research coordinator responsible for recruitment has no control over this. Eligible participants are only determined on the day of, after these assignments have been determined.

iv. Conflict of interest: The PI does not have any affiliation with the sponsor company, DMF Medical Inc. The sponsor and the institution are distinct entities without overlap of responsibilities or business concerns. Although Dr. Schmidt is a staff anesthesiologist and colleague of Dr Hung, Dr. Schmidt has no influence on this study given that he is excluded from participation.

10.2. Participant Confidentiality

Data will be collected directly from the Anesthesia management and nursing management system. All trial records of participants will be kept strictly confidential and will be maintained within NS HEALTHs electronic system. For the purposes of device comparisons there is no requirement that any data points retrieved be linked back to a specific patient identifier. For auditing purposes, or in the event a memsorb participant wishes to have their data excluded from the study, each memsorb data set will de-identified using a unique identifier. A master file will be kept by the Principal Investigator only, which links patient name with unique identifier. Trial data will be kept for 25 years per NS HEALTH's requirements. De-identified trial data will only be made available to the principal investigator and assigned trial personnel as they are identified in this application (CVs appended). Patient participants will not be identified in any reports or publications as a result of participation in this trial. Records may be shown to the NS HEALTH Research Ethics Board in the case of an audit.

10.3. Study Modification/Discontinuation

Participants may withdraw at any time and their information will not be used in the data analysis. The study sponsor, the Nova Scotia Health Research Ethics Board, Health Canada, and the principal investigator have the right to stop patient recruitment or cancel the study at any time. Modifications to this study will be submitted to the NS HEALTH REB as per institutional policy.

11. PUBLICATION OF RESEARCH FINDINGS

Data analyses and publication will be conducted in collaboration between the Principal Investigator and Study Sponsor as outlined in the Contractual Agreement.

12. REFERENCES

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13. **APPENDICES**

13.1. Appendix A: L-SOP-14001 Memsorb Device Installation and Basic Use Training Procedure and Attachment 1

13.2. Appendix B: Feeder List to Delegation and Signature Log