Sevoflurane usage and fresh gas flows in Maquet anaesthetic machines at an academic hospital

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in the partial fulfilment of the requirements for the degree of Master of Medicine in the branch of Anaesthesiology.

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Declaration

I, Aobakwe Robert Setlhare, herewith declare that this research report is my own, unaided work. It is being submitted for the degree of Master of Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

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Signed

20 August 2024

Dedication

This project is dedicated to my beautiful wife, Nokukhanya Mkhize, for her unwavering support and encouragement in my academic research.

Presentations and publications

1. Presentation: none at present
2. Publication: none at present

Abstract

Background

Low-flow anaesthesia (LFA) is an important tool to combat the rising healthcare costs and the global threat of climate change. This study aimed to prospectively analyse the conduct of inhalational anaesthesia at Charlotte Maxeke Johannesburg Academic Hospital to determine fresh gas flows (FGF) and the liquid agent consumption (LAC) at different stages of anaesthesia.

Methods

A prospective, contextual research design was followed. Consecutive convenience sampling was done across ten theatres equipped with Maquet Flow-i® anaesthetic machines. The study included 137 eligible cases. Data were downloaded from the anaesthetic machines and formula-based calculations of LAC were compared to the measured LAC displayed by the anaesthetic machines.

Result

The average FGF during induction, maintenance and time-weighted case average were 7.07, 1.41 and 1.73 l/min respectively. The average end-tidal sevoflurane concentration during maintenance was 2.40%, whilst the average minimum alveolar concentration was 0.90±0.10. The calculated average LAC for induction, maintenance and case were 7.74, 28.01 and 36.84 ml respectively, whilst the hourly LAC was 16.71 ml/h. The calculated case average LAC overestimated the measured values by 4.14±4.86 ml (12.98%), with 98.5% of values being within ±1.96 SD. Despite its brevity (4.6% of total case duration), the induction phase accounted for 21% of the predicted LAC. The predicted liquid agent expenditure over time was ZAR 54.32±23.55/h. Case average FGF had a very high positive correlation with the predicted cost of sevoflurane, $r = 0.86$, $p < 0.001$.

Conclusion

The study demonstrated that anaesthetists at CMJAH conducted medium flow anaesthesia, which correlated with increased sevoflurane consumption. With the average FGF induction of 7.07 l/min, the first strategy in achieving LFA would be to encourage anaesthetists to lower this value to the optimal FGF of 4 l/min when sevoflurane is introduced during induction.

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List of Abbreviations

ACGO	Auxiliary common gas outlet
AM	Anaesthetic machine
ASA	American Society of Anesthesiologists
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CO_2	Carbon dioxide
CO_2e	Carbon dioxide equivalent
ETS	End-tidal sevoflurane
ETT	Endotracheal tube
FGF	Fresh gas flow
GWP	Global warming potential
LAC	Liquid agent consumption
LFA	Low-flow anaesthesia
LMA	Laryngeal mask airway
MAC	Minimum alveolar concentration
SD	Standard deviation
USB	Universal Serial Bus
USD	United States Dollar
WITS	University of the Witwatersrand
ZAR	South African Rand

Statement

The Research Report consists of a literature review, draft article, study proposal and appendices. The study proposal is included for background reference and is not for examination.

The formatting of this Research Report complies with the University of the Witwatersrand's Style Guide for Theses, Dissertations and Research Reports.

The formatting of the draft article is in keeping with the rest of the research report and complies with the author guidelines of the Southern African Journal of Anaesthesia, the journal to which it is intended to be submitted.

Section 1: Review of the literature

1.1 Introduction

The American Association of Anesthesiologists (ASA) defines general anaesthesia as a "drug-induced loss of consciousness, during which patients are not arousable, even by painful stimulation."[1] A combination of drugs is commonly used to achieve a triad of hypnosis, analgesia and muscle relaxation, as opposed to relying on a single drug.[2]

This literature review explores the history, principles and technology behind LFA, highlighting its benefits for patient care and its role in achieving environmental sustainability.

1.2 Low-flow anaesthesia

With the evolution of anaesthesia, techniques are being developed to ensure patient safety and improve outcomes whilst being environmentally friendly. Low-flow anaesthesia (LFA) has emerged as a relatively simple and safe measure to reduce costs and save the environment from the harmful effects of inhalational agents.[3-5] LFA is "An inhalation anaesthetic technique in which the rebreathing fraction at least amounts to 50%, where at least 50% of the exhaled gas mixture is returned to the patient after carbon dioxide (CO_2) removal in the next inspiration."[6] Baker[7] classified fresh gas flow (FGF) in anaesthetic rebreathing circuits according to Table 1.2.1 below.

Table 1.2.1: Classification of flow rates in anaesthetic circle systems

Classification	Flow rate in litres per minute (L/min)
Metabolic flow	0.25
Minimal flow	0.25 – 0.5
Low-flow	0.5 – 1.0
Medium flow	1 – 2
High flow	2 - 4
Very high flow	> 4

1.3 Historical perspective

Although there were multiple instances of individuals administering anaesthetic agents in the 1830s and 1840s, these events were not publicised. It was not until 16 October 1846 that William T.G. Morton performed the first public demonstration of ether anaesthesia at Massachusetts General Hospital.[8] In 1847, John Snow[9] developed a safer anaesthetic practice

with his study on narcotism by the inhalational vapours. He later converted his ether inhaler into a to-and-fro rebreathing system in which CO_2 was absorbed by caustic potash.[8]

In 1869, Alfred Coleman was the first to use a to-and-fro system for CO_2 absorption in clinical practice, where the CO_2 was absorbed using slaked lime.[10] Later, in 1924, Waters developed a to-and-fro system that avoided reabsorption of CO_2 with granular soda lime while Brian Sword then described the circle breathing system with soda lime absorber for closed circuit ventilation.[11] The closed circuit system permitted the usage of very low gas flows with great economy initially; however, with the development of non-rebreathing and semi-closed circuits, the use of high gas flows became common practice.[8] LFA has since seen a resurgence with the need to reduce theatre and environmental pollution and make anaesthesia more economical.[12]

1.4 Principles of inhalational anaesthesia

General anaesthetics include a wide range of intravenous and inhaled drugs that induce a reversible comatose state characterised by unconsciousness, amnesia and immobility.[13] Inhaled anaesthetics are classified into three broad groups: potent halogenated ethers (isoflurane, sevoflurane, desflurane, enflurane) and alkane (halothane) volatile anaesthetics and the inorganic gaseous anaesthetics (nitrous oxide and xenon). The minimum alveolar concentration (MAC) is a measure of inhaled anaesthetic potency. It is defined as the inhaled anaesthetic atmospheric pressure required to prevent movement in response to a defined noxious stimulus in 50% of subjects. In practice, MAC is used by researchers and clinicians as a universal standard for measuring a defined anaesthetic endpoint, which is immobility.[14]

Uptake and elimination of inhaled anaesthetics is through alveolar blood-gas exchange. The drug dosage can be monitored using expired alveolar gas concentration, as tissue-dependent metabolism is unnecessary for drug clearance. The alveolar partial pressure determines anaesthetic uptake into blood and target tissues in the central nervous system. It is influenced by both the delivery and uptake of anaesthetic gas. Inhaled anaesthetic delivery to patients is affected by fresh carrier gas flows, vaporiser output settings and minute ventilation.[15] An anaesthesiologist uses this knowledge to induce the required depth of anaesthesia and the rate at which it is achieved.

A patient under general anaesthesia uses a small fraction of the inhaled anaesthetic. Depending on the breathing circuit, more than 80% of the delivered inhalational agent is wasted when using moderately high FGF.[15] Modern anaesthetic machines utilise rebreathing

circuits that allow for anaesthetic gases to be recycled while exhaled CO_2 is absorbed from the circuit.[16] These rebreathing circuits allow the use of FGF well below minute ventilation, which results in reduced anaesthetic discharge into the waste-scavenging system.[15]

1.5 Low-flow anaesthesia technique

To practice LFA, a good knowledge of potential associated risks is paramount and these include hypoxia, hypercapnia, inadequate depth of anaesthesia and possible accumulation of toxic trace gases.[4] The following equipment is essential for the safe practice of LFA: a leak-free circle breathing system with a CO_2 absorber, two unidirectional valves, a fresh gas inlet, an adjustable pressure limiting valve and a reservoir bag and patient Y-piece connection.[17] Upadya and Saneesh[12] also list the usage of flow meters calibrated down to 50 millilitres per minute (ml/min), well-calibrated vapourisers capable of delivering high concentrations at low FGF and minimal internal volume breathing circuits in addition to the other requirements as mentioned above.

Previously, the recommended minimum FGF for sevoflurane was 1 l/min for anaesthesia durations of up to 1 hour and 2 l/min for those lasting longer than 2 hours due to concerns about compound A renal toxicity.[18] However, using newer generation CO_2 absorbers such as DrägerSorb Free® or Amsorb Plus®, the concentrations of harmful products in the circuit were negligible when using LFA.[19]

LFA requires an initial wash-in period to achieve adequate inhalational agent concentration. A study using a test lung found that it takes roughly 1 minute to increase inhalational agent concentration from 0 to 1 MAC with a vaporiser setting of 3 x MAC (6% sevoflurane) and FGF of 4 – 4.8 l/min with higher FGF not leading to faster wash-in times.[20] Another study proposed a 1-1-8 wash-in scheme for sevoflurane LFA where by O2:Air at 1:1 l/min plus sevoflurane 8% yields inhalational agent concentration of 1, 1.5, 2, 2.5, 3 and 3.5% at 1, 1.5, 2, 3, 4 and 5 minutes respectively.[21] These strategies remain expert opinion as there are no formal guidelines on how to conduct LFA. Welch[22] also provides a practical guide on how to conduct LFA.

With the advent of modern anaesthetic machines, automated control of end-tidal gases markedly reduces the waste, cost and pollution of inhalational anaesthesia while reducing the ergonomic burden of low-flow anaesthesia.[23] In a 2013 Australian study, automated control reduced costs by 27% and lowered greenhouse emissions by 47%, although this was greater than expected due to the proportional decrease in desflurane usage.[24]

1.6 Cost of inhalational anaesthesia

The cost of providing healthcare services, facilities and technologies continues to rise while resources remain finite.[5, 25, 26] This is more evident in developing countries like South Africa, where there is a large demand-supply gap for healthcare services. [27] With this in mind, it is imperative to continually analyse the conduct of inhalational anaesthesia to identify cost-containment measures without compromising patient care.

Economics is a science that analyses how choices are structured and prioritised to optimise decision-making within constrained resources.[28] When this science is used to evaluate pharmaceuticals, it is termed pharmacoeconomic studies.[29] Chaudhry defines pharmacoeconomics as "a branch of economics that uses cost-benefit, cost-effectiveness, cost minimisation, cost-of-illness and cost-utility analyses to compare pharmaceutical products and treatment strategies."[30]

The four frequently used terms in "economic evaluation: cost-effectiveness, cost-utility, cost-minimisation and cost-benefit analysis" are summarised in Table 1.6.1 below.[28, 30, 31]

Table 1.6.1: Types of economic evaluation

Type of economic evaluation	Measurement and valuation outcome
Cost-effectiveness analysis	Compares cost against measured risk or benefits which are not converted to monetary units related to health effects
Cost-utility analysis	Compares costs against benefits in terms of quality-adjusted life years (QALYs)
Cost-minimisation analysis	All benefits are considered equal and the focus is to identify the least expensive therapy/intervention
Cost-benefit analysis	Compares the total expected costs against the total expected benefits in monetary terms

There are various costs associated with providing anaesthesia, including but not limited to staff salaries, hospital overhead costs, equipment and medication costs.[32] Of these costs, anaesthesiologists have direct control over the prescription and administration of anaesthetic medications. In a 2012 study by Rinehardt and Sivarajan,[32] they found that "anaesthesia medications comprise 10 – 13 % of pharmacy budgets and with the adoption of voluntary protocols to reduce wastage, there was a potential of saving between US$ 350 million – US$ 750 million annually in the United States of America." Regarding inhalational anaesthetic

agents, it is estimated that they account for 20 – 25% of the total anaesthetic drug cost. [3, 5, 33] Thus, cost-containment and awareness programs would be highly beneficial as it has been shown that only 22% of anaesthesia providers can accurately estimate the cost of commonly used medications, supplies and blood products.[34]

Multiple international studies that discuss various costs of anaesthesia care have been published; however, very few provide a South African perspective. To the best of our knowledge, the only published South African study that addressed the cost of inhalational anaesthesia was by Ryksen and Diedericks[35] in 2014. Their study compared the theoretical costs of different anaesthetic techniques of various anaesthesia durations. The main challenge of their research was that it was difficult to extrapolate their findings to clinical practice. The required depth of anaesthesia varies between patients and in an individual patient.

Additionally, within an individual patient, the degree of surgical stimulation and administration of other intravenous anaesthetic drugs greatly influences the depth of anaesthesia. As a result, in clinical practice, the anaesthesiologist would adjust the vaporiser and FGF setting to account for these variations. The strict time intervals used in their inhalational protocol are unlikely to be followed in clinical practice. Therefore, a cost analysis of current clinical practices is necessary for a more holistic South African perspective. This need is further supported by a survey that found South African healthcare practitioners lack awareness of the costs of disposables, tests and drugs commonly used in their practice.[36]

1.7 Benefits of low-flow anaesthesia

Potential benefits of LFA include preservation of the patient's heat and humidity.[37-39] A 1994 study by Kleemann[38] found that minimal FGF was the best way to improve airway climate with humidity of > 20 milligrams of water per litre (mg H_2O/l) obtained after an hour of anaesthesia. Braz et al.[39] confirmed these findings with a 2017 systematic review and meta-analysis of 10 randomised controlled trials. This improved airway humidity and temperature may decrease deleterious effects of prolonged inhalation of dry gases such as, impaired ciliated epithelium functioning, induction of inflammation, predisposition to atelectasis or pneumonia and hypothermia.[4] Other physiological advantages of LFA include conservation of body temperature, reduced dehydration and improved inhaled gas flow dynamics.[12]

LFA also has ecological and environmental benefits as it reduces the emission of inhalational anaesthetic gases, which deplete the ozone layer and cause greenhouse effects.[12, 22] The environmental impact of anaesthetic gases is often reported in terms of global warming

potential (GWP). GWP is a measure of the radiative efficiency and atmospheric lifetime of a given mass of gas and compares it on a relative scale to the same mass of CO_2.[40, 41] Anaesthetic agents last significantly longer in the atmosphere than CO_2. As a result, the 100-year GWP is often reported. Desflurane has the longest 100-year GWP at 2540 units, followed by isoflurane at 510 units, nitrous oxide at 298 units and sevoflurane at 130 units.[33, 40, 42, 43] For a simplified perspective, an hour of anaesthesia with FGF of 0.5 – 2 L/min is equivalent to driving 18 miles (28 kilometres) in a car using sevoflurane, 20 – 40 miles (32 – 64 kilometres) with isoflurane and 235 – 470 miles (378 – 756 kilometres) with desflurane. [44] The use of nitrous oxide also significantly increases the carbon footprint of sevoflurane and isoflurane anaesthesia.[44]

Economic advantages of LFA include reduced inhalational gas consumption. In a study by Edmonds et al.,[33] an estimated US$ 96,960 was spent on sevoflurane, isoflurane and desflurane for cases in the study. Using predictive simulation analysis, they found that an average FGF of 1 L/min could yield a 48% reduction in the cost of various inhalational anaesthetics. In another study by Ryu et al.,[45] reported savings in terms of the number of anaesthesia hours performed per bottle of sevoflurane and they saw a 38.3% increase following the implementation of policy advocating for LFA.

1.8 Challenges of low-flow anaesthesia

Several challenges are associated with LFA, including long time constants with slow induction and emergence, the need to continuously be vigilant and frequent manual adjustments to avoid under/over-dosage and high CO_2 absorbent consumption.[12] Some of these challenges are mitigated using automated end-tidal gas control, which has been proven to be safe, efficient and lowers the burden of conducting LFA.[23] A 2020 systematic review and meta-analysis of randomised controlled trials showed that concerns about toxic substances with sevoflurane LFA are unwarranted and the scientific basis recommending high FGF needs review.[46] These findings are further supported by a 2023 study that found that during on-pump cardiac surgery with sevoflurane anaesthesia, minimal FGF rate was not associated with an increased risk of postoperative acute kidney injury in this population already at high risk for renal injury.[47]

Promoting LFA through increasing awareness has been shown to decrease overall expenditure on inhalational agents without affecting patient care.[48] To maintain the use of LFA, ongoing feedback is necessary to sustain a behaviour change.[5, 49]

A significant challenge in a resource-limited setting is that most public hospitals lack the necessary resources to acquire and maintain electronic record-keeping software and hardware. Thus, auditing current clinical practices and implementing the quality improvement measures needed to achieve cost-effective and environmentally sustainable anaesthesia is challenging.

In 2014, Biro[50] presented a method of calculating volatile anaesthetic consumption retrospectively and prospectively using agent concentration and fresh gas flow. This calculation method was later validated to be sufficiently accurate in estimating the economic impact of inhalational anaesthetic delivery.[51] These studies provide the basis for this research.

1.9 Summary

Studies have shown that LFA reduces inhalational anaesthesia's financial cost and environmental impact without compromising patient care. All the equipment required to practice LFA safely is already in clinical use. There is a current lack of awareness of LFA and a need exists to promote its usage continuously and achieve sustained behavioural change.

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Section 2: Authors guidelines

Southern African Journal of Anaesthesia and Analgesia (SAJAA)

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Acknowledgements

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Section 3: Draft Article

Sevoflurane usage and fresh gas flows in Maquet anaesthetic machines at an academic hospital

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Keywords: sevoflurane, low-flow anaesthesia, cost, cost-containment, Maquet Flow-i®, environment, South Africa

Abstract

Background

Low-flow anaesthesia (LFA) is an important tool to combat the rising healthcare costs and the global threat of climate change. This study aimed to prospectively analyse the conduct of inhalational anaesthesia at Charlotte Maxeke Johannesburg Academic Hospital to determine fresh gas flows (FGF) and the liquid agent consumption (LAC) at different stages of anaesthesia.

Methods

A prospective, contextual research design was followed. Consecutive convenience sampling was done across ten theatres equipped with Maquet Flow-i® anaesthetic machines. The study included 137 eligible cases. Data were downloaded from the anaesthetic machines and formula-based calculations of LAC were compared to the measured LAC displayed by the anaesthetic machines.

Result

The average FGF during induction, maintenance and time-weighted case average were 7.07, 1.41 and 1.73 l/min respectively. The average end-tidal sevoflurane concentration during maintenance was 2.40%, whilst the average minimum alveolar concentration was 0.90±0.10. The calculated average LAC for induction, maintenance and case were 7.74, 28.01 and 36.84 ml respectively, whilst the hourly LAC was 16.71 ml/h. The calculated case average LAC overestimated the measured values by 4.14±4.86 ml (12.98%), with 98.5% of values being within ±1.96 SD. Despite its brevity (4.6% of total case duration), the induction phase accounted for 21% of the predicted LAC. The predicted liquid agent expenditure over time was ZAR 54.32±23.55/h. Case average FGF had a very high positive correlation with the predicted cost of sevoflurane, $r = 0.86$, $p < 0.001$.

Conclusion

The study demonstrated that anaesthetists at CMJAH conducted medium flow anaesthesia, which correlated with increased sevoflurane consumption. With the average FGF induction of 7.07 l/min, the first strategy in achieving LFA would be to encourage anaesthetists to lower this value to the optimal FGF of 4 l/min when sevoflurane is introduced during induction.

Introduction

The cost of providing healthcare services, facilities and technologies continues to rise whilst resources remain finite.[1-3] This is evident in developing countries like South Africa, where a large demand-supply gap exists for healthcare services.[4] As a result, it is imperative that hospitals implement cost-containment measures without compromising patient care.

One measure of potential cost reduction involves the usage of volatile anaesthetics (VA). In the United States of America, anaesthesia medications account for 10 – 13 % of pharmacy budgets, according to Rinehardt and Sivarajan.[5] With the adoption of voluntary protocols to reduce wastage, they further note a potential to yield savings of US$ 350 million – US$ 750 million annually. It is estimated that VA accounts for 20% of the total anaesthetic drug cost.[6] Therefore, implementing cost-containment and awareness programmes would be advantageous due to the low cost-consciousness among healthcare providers.[7, 8]

Low-flow anaesthesia (LFA) has been shown to have a significant potential to save costs and reduce the environmental impact of VA.[9-11] Despite their small contribution to greenhouse gases, it is essential to minimise the release of waste anaesthetic gases into the environment.[12] Advances in anaesthesia machines and carbon dioxide absorbents allow anaesthetists to practice LFA with improved margins of safety and ease.[13, 14]

The key determinants of overall fresh gas flow (FGF) and liquid agent consumption (LAC) under the anaesthetist's direct control are induction FGF, induction duration and maintenance FGF.[15] Although very important in overall LAC, the maintenance duration is beyond the control of the anaesthetist. Numerous international studies that discuss various costs of anaesthesia care have been published.[1, 5, 16] However, to the best of our knowledge, the only published South African study that addressed the cost of inhalational anaesthesia was by Ryksen and Diedericks in 2014.[17]

This study aimed to prospectively analyse the conduct of inhalational anaesthesia at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) to determine FGF and the LAC at different stages of anaesthesia**.**

Methods

Approval was obtained from the Human Research Ethics Committee, the Post Graduate Committee (Medical) of the University of the Witwatersrand and other relevant authorities, study number M230147. A prospective, contextual research design was followed.

The study was conducted from 15/05/2023 to 26/05/2023. The study population consisted of data logs from Maquet Flow-i® anaesthetic machines (AM) at CMJAH. This model was selected as it was the sole anaesthetic machine at our institution capable of exporting data logs directly to a Universal Serial Bus (USB) drive without the need for additional proprietary software or licensing. Purposive sampling method was used. Based on biostatistical calculations to compare a single cohort's continuous mean primary outcome against a literature-derived standard, a minimum sample size of 105 cases was determined to achieve an alpha of 0.05 and a power of 95%."

All data from elective and emergency general anaesthetic cases conducted with a Maquet Flow-i® AM throughout the study period, weekends included, were collected. Cases that used closed circuit ventilation with either a laryngeal mask airway or endotracheal tube, lasted longer than 45 minutes in duration and used sevoflurane as the sole VA, were included in the study. In all cases where an auxiliary common gas outlet (ACGO) was used, maintenance minimum alveolar concentration (MAC) of less than 0.7 or AM with a leak greater than 150 ml/min were excluded from the study.

Data were collected at the end of each elective theatre list and 12 hourly for emergency theatres by inserting a USB drive into the rear USB port by the primary researcher. The primary was not present during any if the cases. The menu button was selected. The save all data logs and trends to USB were selected using the touch interface. The saved data were then consolidated into a single Microsoft Excel® spreadsheet. Cases were identified by continuous data logs recorded at one-minute intervals. Any data entry break longer than ten minutes was considered the end of a case, with subsequent entries being the start of another. There were no missing data. Cases that met the inclusion criteria were identified and analysed further.

The phases of anaesthesia were defined as follows: the induction phase, where FGF was greater than or equal to 5 l/min, the transition phase, where FGF was greater than or equal to 2 l/min but less than 5 l/min and the maintenance phase, where FGF was less than 2 l/min and ended when the vaporiser was turned off.[15] Movement between phases was unidirectional,

which meant that once the maintenance phase was entered, all subsequent adjustments formed part of maintenance regardless of the FGF. The ambient theatre temperatures and barometric pressures were recorded at 11h00 and 14h00 daily. This process was repeated in all ten theatres.

The first step was to determine the saturated gas volume using the formula below:[18]

$$Saturated\ Gas\ Volume\ (ml/ml) = \frac{specific\ weight^{1}.Avogadro's\ gas\ constant^{2}.(273+temperature)^{3}}{molecular\ weight^{4}.273}$$

1. Specific weight of sevoflurane = 1.53 grams per millilitre (g/ml)
2. Avogadro's gas constant states that at a standard atmospheric pressure of 760 mmHg (at sea level) and at a temperature of 0 °C = 273 Kelvin (°K) one mole of any gas consists of 6.023 x 10^{23} molecules, which in turn occupy a volume of 22,400 ml. This is the same for all gases, VA included, at standard temperature, standard pressure and dry conditions.
3. Temperature of vaporiser = room temperature – 2 ºC due to loss of energy during evaporation
4. Molecular weight of sevoflurane = 200.

The calculations accounted for the elevation of Johannesburg, 1760 metres above sea level,[19] and daily barometric pressures when calculating Avogadro's gas constant. Daily ambient theatre temperatures were used in the formula. The saturated gas volume obtained was then used to calculate the fluid volatile agent consumed per time segment as shown below:[18]

$$fluid\ volatile\ agent\ (ml) = \frac{FG\ flow\left(\frac{ml}{\min}\right).VA\ conc.(Vol\%).Anaesthesia\ duration\ (\min)}{Saturated\ gas\ volume\left(\frac{ml}{ml}\right).100(Vol\%)}$$

Abbreviations:

- FG - fresh gas
- VA conc. - volatile anaesthetic concentration
- Vol – volume
- ml/min - millilitres per min
- min – minute

The calculated volumes per time segment were then summed up to get the total volumes per phase of anaesthesia and for the entire duration of the anaesthetic. To verify accuracy of calculated volumes, they were compared to the measured values recorded by the AM. The

procurement cost of sevoflurane as per government tender in May 2023 was used to determine predicted costs.

Data were exported to IBM SPSS 28® for analysis. The majority of the results were descriptive results. Pearson correlation and regression analysis were used to explore the relationship between predicted and measured values. Overall FGF was calculated using time-weighted means to enable comparison with other published literature. Similar to a study by Kennedy et al.,[15] the underlying data may not be normally distributed, however, this value represented the average FGF and, therefore LAC. The flow rates at different stages of anaesthesia were described with the median, interquartile range and 85th centile to quantify outliers. The relationship between liquid agent consumption and case average FGF was also explored using linear regression analysis.

Results

The study recruitment flow diagram in Figure 1 was used for case selection. In total, 211 sevoflurane general anaesthesia cases were performed in ten operating theatres using Maquet Flow-i® AM.

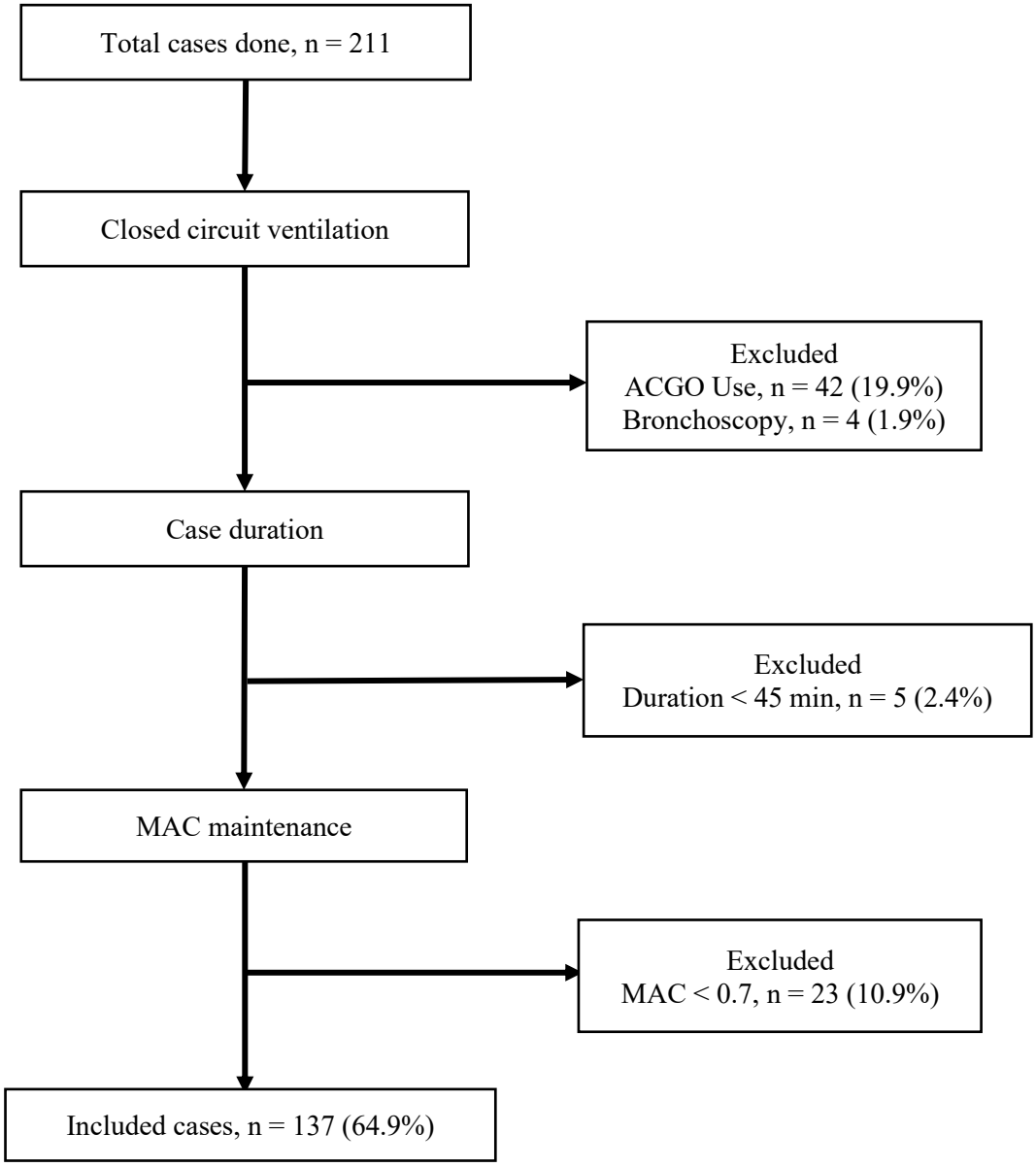

Figure 1: Case selection flow diagram

Table I: Pattern of fresh gas flows rates at various phases of anaesthesia, average MAC and Maintenance ETS

	Induction FGF (l/min)	Induction duration (min)	Maintenance FGF (l/min)	Case average FGF (l/min)	Average MAC	Average maintenance ETS (%)
Mean (SD)	7.07 (1.83)	6.69 (5.73)	1.41 (0.7)	1.79 (0.73)	0.90 (0.1)	2.40 (0.42)
Minimum	0.00	0.00	0.68	0.93	0.71	1.52
25th centile	6.00	3.00	1.03	1.27	0.82	2.11
50th centile	6.52	6.00	1.17	1.61	0.90	2.38
75th centile	8.00	9.00	1.55	2.08	0.96	2.62
85th centile	9.00	11.00	1.91	2.30	1.00	2.80
Maximum	12.90	39.00	6.23	6.21	1.24	3.84

Abbreviations: SD – Standard deviation, ETS – End-tidal sevoflurane, FGF – Fresh gas flow and MAC – Minimum alveolar concentration

Inhalational agent concentration during the maintenance period was found to be most representative of the depth of anaesthesia maintained in our study. The distribution of average maintenance end-tidal sevoflurane (ETS) across all theatres is shown in Table I. The paediatric theatres 1 and 2 demonstrated significantly higher average ETS (2.94% and 2.99%, respectively) compared to other theatres ($p < 0.001$), except theatre 6 (2.57%) which accommodates both paediatric and adult cases ($p = 0.500$ and $p = 0.061$respectively).

These ETS concentrations corresponded with an average maintenance MAC value of 0.90±0.10 across all theatres. The one-way ANOVA test showed a significant difference in MAC across theatres, $F (9, 127) = 1.97$, $p = 0.048$. Tukey's post-hoc test was used to compare the groups in pairs to determine which was significantly different. Despite the significant difference in the ANOVA, no pairwise group comparison was significant in Tukey's post-hoc test; all p values were greater than 0.05.

The distribution of average FGF for induction, maintenance and overall case are shown in Table I. Sevoflurane was administered for a total of 19,969 minutes. This time was distributed as follows: induction (916 minutes, 4.6%), transition (328 minutes, 1.6%), and maintenance (18,725 minutes, 93.8%). The average transition phase duration was 2 minutes per case. Given the relatively short duration of the transition phase (1.6% of total time), further analysis of this phase was deemed unnecessary. This period was however included when calculating case average FGF for each case.

The results for average FGF at induction, maintenance and overall case average FGF are depicted in Figure 2. Average FGFs were pooled because the one-way ANOVA test showed no significant differences in case average FGF across theatres $F(9, 127) = 1.040$, $p = 0.412$. The case average FGF, 1.79±0.73 l/min, summarises the mean of the individual cases. This value is independent of the individual case duration and therefore, differs from the time-weighted pooled mean of 1.73 l/min. Paired t-test analysis showed that case average FGF was significantly higher than maintenance FGF, $p < 0.001$.

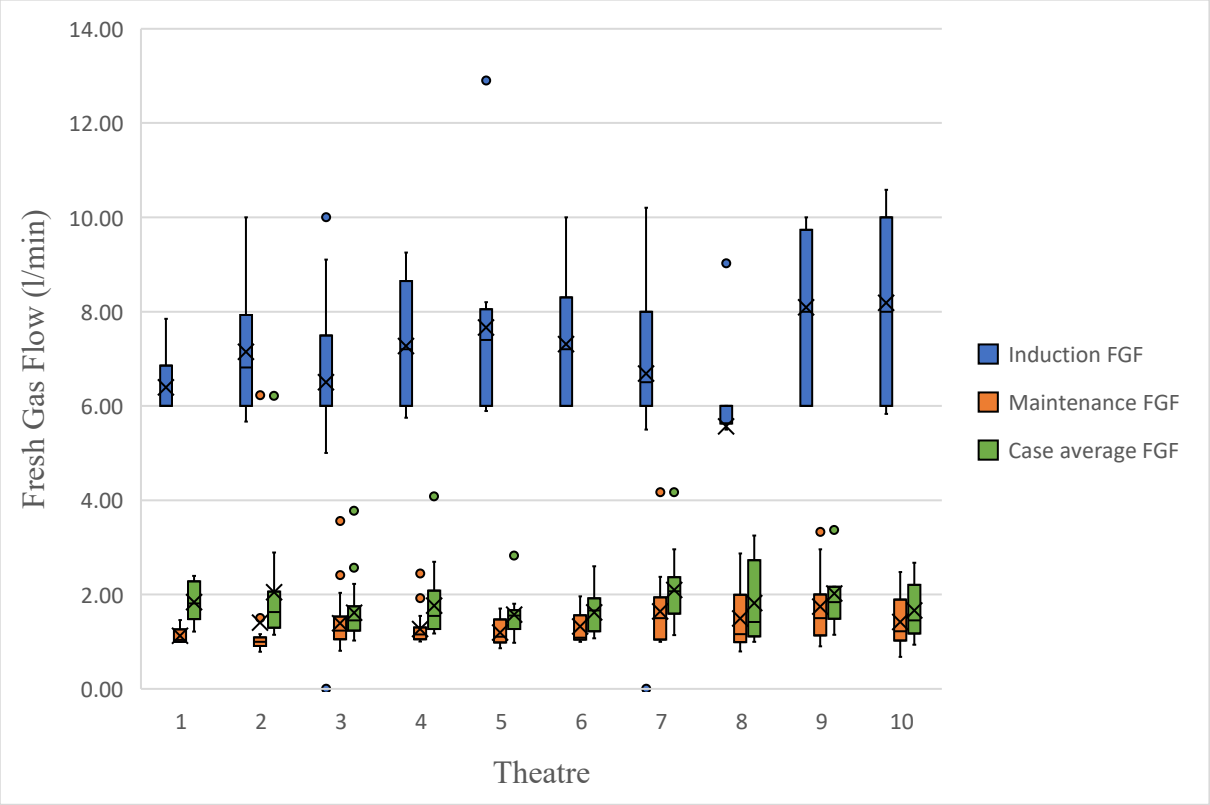

Figure 2: Theatre fresh gas flows per time segment

The average calculated LAC for induction, maintenance and case total are shown in Table II. One-way ANOVA test showed no significant difference in total calculated LAC across theatres, $F(9, 127) = 1.58$, $p = 0.127$, therefore results were pooled. The Pearson correlation in Figure 3 showed a significant correlation between total calculated and measured LAC, $r = 0.977$, $p < 0.001$. The regression model showed that measured LAC explained 95.5% ($R^2 = 0.955$) of the variance in calculated LAC, $F(1, 135) = 2865.63$, $p < 0.001$. Measured LAC was a significant predictor of calculated LAC, $\beta = 1.099$, $p < 0.001$. In the Bland/Altman analysis of pairs shown in Figure 4, 135 (98.5%) of the values were within the ±1.96 SD. The average measured LAC was 32.69±18.82 ml, whereas the calculated consumption showed a systematic average overestimation by 4.14±4.86 ml (12.98±10.41%).

The total calculated LAC across all theatres was 5 046.49 ml, with 1 060.07 ml in induction and 3 837.08 ml in maintenance. This was higher than the measured LAC of 4 479.10 ml. While the induction phase is relatively short (4.6% of the total), its LAC was substantial, accounting for 21% of the predicted LAC. The cost of sevoflurane was determined using the 2023 government procurement cost of ZAR 813.46 per 250 ml bottle, or approximately ZAR 3.25/ml. Across all theatres during the study period, the total expenditures for calculated LAC, induction, maintenance, and measured LAC were ZAR 16 401.10, ZAR 3 445.23, ZAR 12 470.51, and ZAR 14 557, respectively.

Table II: Liquid agent consumption and expenditure

	Sevoflurane n = 137
Calculated Induction LAC (ml)	7.74 (6.91)
Calculated Maintenance LAC (ml)	28.01 (20.43)
Total Calculated LAC (ml)	36.84 (21.17)
Measured LAC (ml)	32.69 (18.82)
Difference to control (ml)	4.14 (4.86)
Difference to control (%)	12.98 (10.41)
LAC duration (min)	145.76 (95.42)
Predicted induction LAC over time (ml/min)	1.15 (0.51)
Predicted maintenance LAC over time (ml/min)	0.21 (0.1)
Predicted case average LAC over time (ml/h)	16.71 (7.25)
Predicted average case cost (ZAR)	119.72 (68.79)
Predicted average case cost over time (ZAR/h)	54.32 (23.55)

LAC – Liquid agent consumption

ZAR – South African Rand

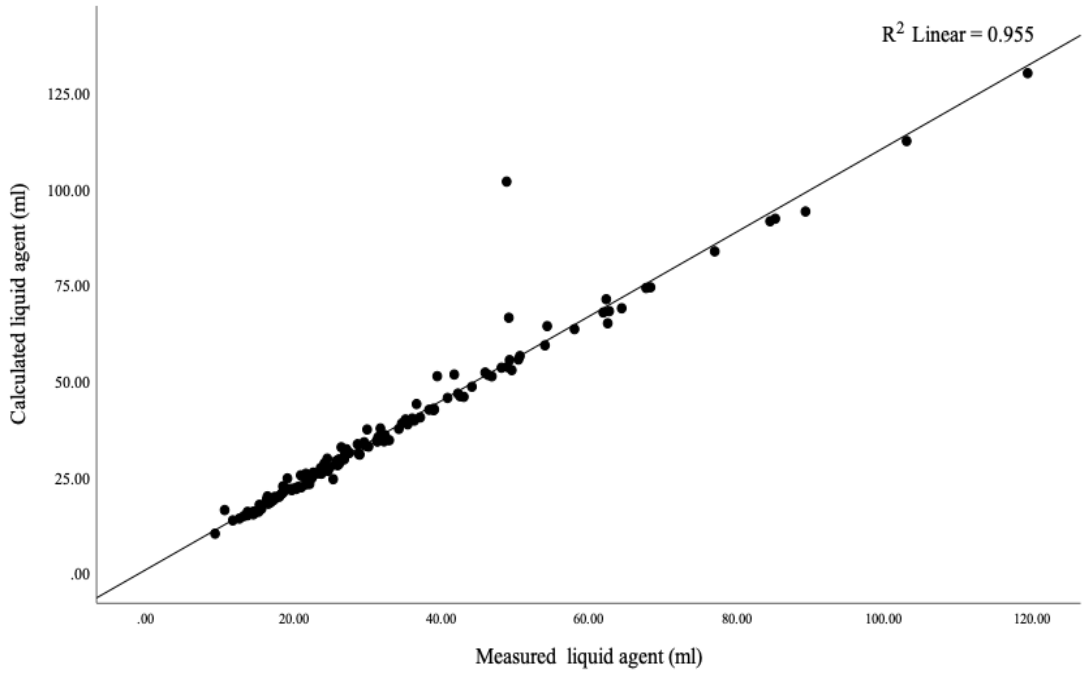

Figure 3: Linear correlation of calculated vs measured liquid agent consumption

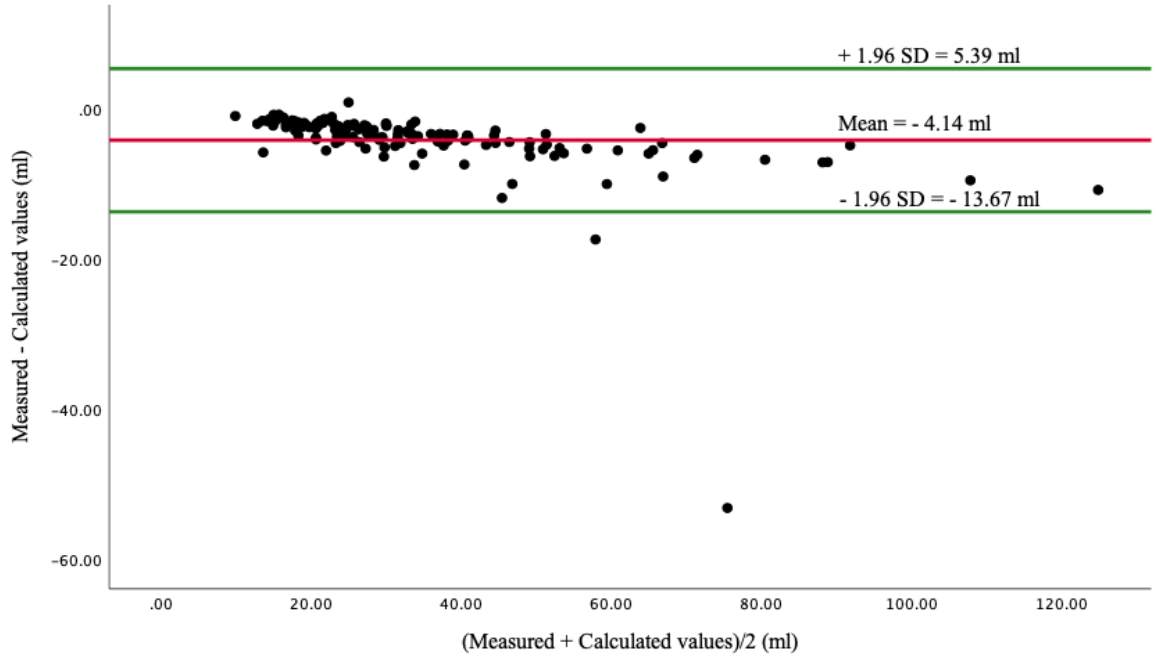

Figure 4: Bland/Altman analysis of calculated vs measured liquid agent consumption

The case average FGF had a very high positive correlation with the predicted cost of sevoflurane, r = 0.86, p < 0.001. The line of best-fit equation was ml of sevoflurane per minute = 0.02 + 0.14*x. The regression model showed that the case average FGF explained 74.15% of the variance in predicted LAC over time, which is, therefore, expenditure. The ANOVA test showed that the regression model was statistically significant, F (1,135)

=387.29, $p < 0.001$, $R^2 = 0.741$. Another factor that had a high positive correlation to predicted expenditure was the maintenance FGF, $r = 0.65$. Factors such as induction FGF, maintenance ETS and MAC had no significant or low positive correlation with the predicted sevoflurane expenditure.

Discussion

Inhalational anaesthetic gases exert their physiological effects in proportion to their partial pressure, which remains constant at various altitudes.[20] Despite measuring partial pressure, gas analysers are calibrated in percentages, which can lead to dosing errors.[21] Whilst vaporiser output remains constant, measured concentration increases with decreasing barometric pressure.[21] According to James,[20] the recommended ETS concentration at an altitude of 1 524 m is 2.4%, which is the same average value obtained in our study. This shows that the appropriate depth of anaesthesia was maintained. Paediatric theatres (1 and 2) had higher ETS concentrations as expected because younger patients typically require higher concentrations than adults.[22] The average ETS was however The average maintenance MAC was 0.90±0.10. The accuracy of this MAC value relied heavily on anaesthetists entering the correct patient age, a task done inconsistently, thus raising concerns about its reliability in our study.

Similar to findings by Kennedy et al.,[15] published literature often excluded the initial high FGF period associated with the induction phase of anaesthesia. Our study included this initial period to obtain a comprehensive assessment of sevoflurane consumption. The significance is seen with the case average FGF (1.79 l/min) being statistically significantly higher than the average maintenance FGF (1.41 l/min), $p < 0.001$. Our time-weighted average FGF was 1.73 l/min. This value was significantly higher than the case average FGF published by Kennedy et.al[15] during various phases of their study. Our study's higher case average FGF was due to higher induction FGF and the induction period being more than twice as long. Our average maintenance FGF was also more than double those reported in their study.

Leijonhufvud et al.,[23] found that induction FGF of 4 l/min at 3 MAC vaporiser setting (6%) was optimal in increasing VA concentration from 0 to 1 MAC value within a minute. Although Leijonhufvud et al.[23] used a test lung, their findings that time to reach 1 MAC plateaued at FGF of 4 – 5 l/min were significant and supported work done by Mapleson.[24] A 1-1-8 wash-in scheme proposed by Tribuddharat et al.,[25] showed that the initial high FGF period might not be necessary as VA concentrations of 1 to 3.5% used in daily practice can be achieved within 5 minutes using total FGF of just 2 l/min. With our average induction FGF of

7.07 l/min, the first strategy in achieving LFA can be to encourage our anaesthetists to lower this value by using an optimal FGF of 4 l/min. This would be equivalent to approximately 43% reduction in FGF with significant potential cost savings and reduction in environmental pollution. The 25th centile for induction FGF was 6 l/min. With the default set FGF of 6 l/min, most of our anaesthetists increase this FGF to preoxygenate patients but fail to lower FGF once VA is switched on.

The induction duration of the 50th and 75th centiles in our study were 6 and 9 minutes respectively. A significant proportion of anaesthetists kept FGF high longer than required. Our induction durations are in stark contrast to those by Kennedy et al.,[15] whereby 75% of their cases had induction times less than 4 minutes. They also suggested induction durations of 3 – 5 minutes as a reasonable and attainable target. Implementing LFA cost-containment and awareness programmes is therefore imperative as there is a need to reduce induction FGF and duration at our institution.

Due to the lack of an integrated anaesthesia electronic record-keeping solution, work done by Biro[18] to estimate our LACs using VA concentration and FGF was used. A very high positive correlation existed between our predicted and measured values (figure 3). Our predicted LAC overestimated by 4.14±4.86 ml, representing 12.98±10.41% (figure 4). Overall, 98.5% of the predicted LAC values were within ±1.96 SDs of the measured value. This is similar to findings by Biro et al.,[26] showing agreement between our predicted and measured values. However, unlike in their study, our calculations overestimated rather than underestimated the true values.

The predicted average LAC was 16.71±7.25 ml/h, which equates to ZAR 54.32±23.55/h. Using our model, sevoflurane (ml/min) = 0.02 + 0.14 x FGF (l/min), at case average FGF of 0.75 – 1 l/min, we predict an hourly sevoflurane consumption of 7.5 - 9.6 ml/h respectively. Efforts to reduce the current time-weighted average FGF from 1.73 l/min to 0.75 - 1 l/min could potentially yield a 39 – 52% reduction in the hourly consumption of sevoflurane. With extensive education and behavioural changes, these savings could be higher as our study excluded open circuit cases where FGF and LAC tend to be significantly higher.

In our hospital, we estimate that 12 600 volatile anaesthesia cases are performed annually, with an average case duration of 140 minutes. The current annual pharmacy spending on sevoflurane is ZAR 1 541 412 or approximately 474 280 ml of sevoflurane. A 39 – 52%

saving would potentially reduce annual expenditure by ZAR 601 150 – 801 534 (USD 31 600 – 42 200). Using equations by Edmonds et al.,[27] we estimate that our hospital could reduce pollution by 15 798 – 21 065 kg carbon dioxide equivalent (CO_2e) sevoflurane annually. The potential cost savings and reduced environmental pollution warrant urgent implementation of LFA practice in our hospital.

This study has determined the conduct of inhalational anaesthesia in a South African tertiary hospital and successfully identified potential cost savings and waste reduction areas. Despite being a single-centre study, this does not limit the generalisability of its findings, which shows a need to teach the principles of LFA. Potential study limitations include the unknown Maquet® vaporiser performance at different FGF rates.[28] This might explain the discrepancy in our calculated vs measured LAC values. While directly weighing the vaporiser offered a more accurate approach, implementing it within the study would have resulted in insurmountable logistical obstacles, ultimately rendering it impractical. The one-minute data intervals limited the accuracy of the results; however, the impact on clinical interpretation is likely negligible. Another postulated cause for overestimation was the lack of a well-calibrated barometer in theatre. However, this effect in our calculations was minimal as we found that significant changes in the reported barometric pressures yielded minimal change (< 0.5 ml) in the calculated LAC. Theatre temperature variations were also found to have insignificant changes to our calculated consumption. Despite these limitations, our approach is reliable and suitable for pharmacoeconomic estimations.

Conclusion

In this study, we determined FGF at various phases of anaesthesia, VA concentration and MAC across multiple theatres in our hospital. We have reliably predicted LAC and shown that case average FGF is the most important determinant of overall consumption. Through our model, we can reasonably predict potential cost savings and pollution reduction when lower case average flows are targeted. The current climate emergency demands immediate, sustainable and comprehensive efforts to reduce greenhouse gas emissions across all sectors of society to avert its devastating effects on human health, food security and the biosphere.[29] The financial benefits of LFA, coupled with its reduced environmental impact, allow anaesthesiologists to also play an essential role in reducing the effects of climate change.

Conflict of interest

The authors declare no conflict of interest. No funding was received to complete this study.

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Section 4: Proposal

Sevoflurane usage and fresh gas flows in Maquet anaesthetic machines at an academic hospital

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4.1 Introduction

The cost of providing healthcare services, facilities and technologies continues to rise whilst resources remain finite.[1-3] This is more evident in developing countries like South Africa, where there is a large demand-supply gap for healthcare services.[4] With this in mind, this study aims to analyse the conduct of inhalational anaesthesia at a tertiary hospital to identify cost-containment measures without compromising patient care.

Economics is a science that analyses how choices are structured and prioritised to optimise decision-making within constrained resources.[5] When this science is used to evaluate pharmaceuticals, it is termed pharmacoeconomic studies.[6] Chaudhry[7] defines pharmacoeconomics as "A branch of economics that uses cost-benefit, cost-effectiveness, cost minimization, cost-of-illness and cost-utility analyses to compare pharmaceutical products and treatment strategies."

The four frequently used terms in "economic evaluation: cost-effectiveness, cost-utility, cost-minimisation and cost-benefit analysis" are summarised in Table 4.1.1 below.[5, 7, 8]

Table 4.1.1: Types of economic evaluation

Type of economic evaluation	Measurement and valuation outcome
Cost-effectiveness analysis	Compares cost against measured risk or benefits which are not converted to monetary units related to health effects
Cost-utility analysis	Compares costs against benefits in terms of quality-adjusted life years (QALYs)
Cost-minimisation analysis	All benefits are considered equal and the focus is to identify the least expensive therapy/intervention
Cost-benefit analysis	Compares the total expected costs against the total expected benefits in monetary terms

There are various costs associated with providing anaesthesia and these include but are not limited to staff salaries, hospital overhead costs, equipment and medication costs.[9] Of these costs, anaesthesiologists have direct control over the prescription and administration of anaesthetic medications. In a 2012 study by Rinehardt and Sivarajan,[9] it was found that anaesthesia medications 10 – 13 % of pharmacy budgets and with the adoption of voluntary protocols to reduce wastage, there was a potential of saving between US$ 350 million – US$ 750 million annually in the United States of America. Regarding inhalational anaesthetic

agents, studies estimate that they account for 20 – 25% of the total anaesthetic drug cost.[3, 10, 11] Thus, cost-containment and awareness programs would be highly beneficial as it has been shown that only 22% of anaesthesia providers can accurately estimate the cost of commonly used medications, supplies and blood products.[12]

Multiple international studies that discuss various costs of anaesthesia care have been published, however, very few provide a South African perspective. To the best of our knowledge, the only published South African study that addressed the cost of inhalational anaesthesia was by Ryksen and Diedericks in 2014. The study compared the theoretical costs of different anaesthetic techniques of various anaesthesia durations.[13] The main challenge of their research was that it was difficult to extrapolate their findings to clinical practice. The required depth of anaesthesia varies between patients and in an individual patient. Additionally, within an individual patient, the degree of surgical stimulation and administration of other intravenous anaesthetic drugs greatly influences the depth of anaesthesia. As a result, in clinical practice, the anaesthesiologist would adjust the vaporiser and fresh gas flow (FGF) setting to account for these variations. The strict time intervals used in their inhalational protocol are unlikely to be followed in practice. Therefore, a cost analysis of current clinical practices is necessary for a more holistic South African perspective. This need is further supported by a survey that found that South African healthcare practitioners lack awareness of the costs of disposables, tests and drugs commonly used in their practice.[14]

General anaesthetics include a wide range of intravenous and inhaled drugs that induce a reversible comatose state characterised by unconsciousness, amnesia and immobility.[15] Inhaled anaesthetics are classified into three broad groups: potent halogenated ethers (isoflurane, sevoflurane, desflurane, enflurane) and alkane (halothane) volatile anaesthetics and the inorganic gaseous anaesthetics (nitrous oxide and xenon). The minimum alveolar concentration (MAC) is a measure of inhaled anaesthetic potency. It is defined as the inhaled anaesthetic atmospheric pressure required to prevent movement in response to a defined noxious stimulus in 50% of subjects. In practice, MAC is used by researchers and clinicians as a universal standard for measuring a defined anaesthetic endpoint which is immobility.[16]

Uptake and elimination of inhaled anaesthetics is through alveolar blood-gas exchange. The drug dosage can be monitored using expired alveolar gases concentration, as tissue-dependent metabolism is unnecessary for drug clearance. The alveolar partial pressure determines anaesthetic uptake into blood and target tissues in the central nervous system. It is influenced by both the delivery and uptake of anaesthetic gas. Inhaled anaesthetic delivery to patients is

influenced by fresh carrier gas flows, vaporiser output settings and minute ventilation.[17] An anaesthesiologist uses this knowledge to induce the required depth of anaesthesia and the rate at which it is achieved.

A patient under general anaesthesia uses a small fraction of the inhaled anaesthetic. Depending on the breathing circuit, more than 80% of the delivered inhalational agent is wasted when using moderately high FGF.[17] Modern anaesthetic machines utilise rebreathing circuits that allow anaesthetic gases to be recycled whilst exhaled carbon dioxide is absorbed from the circuit.[18] These rebreathing circuits allow the use of FGF well below minute ventilation, which results in reduced anaesthetic discharge into the waste-scavenging system.[17]

Low-flow anaesthesia (LFA) has emerged as a relatively simple and safe measure to reduce costs and save the environment from the harmful effects of inhalational agents.[3, 11, 19] It is defined as "An inhalation anaesthetic technique in which the rebreathing fraction at least amounts to 50%, where at least 50% of the exhaled gas mixture is returned to the patient after CO_2 removal in the next inspiration."[20] Baker[21] classified FGF in anaesthetic rebreathing circuits according to Table 4.1.2.

Table 4.1.2: Classification of flow rates in anaesthetic circle systems

Classification	Flow rate in litres per minute (L/min)
Metabolic flow	0.25
Minimal flow	0.25 – 0.5
Low-flow	0.5 – 1.0
Medium flow	1 – 2
High flow	2 - 4
Very high flow	> 4

To practice LFA, a good knowledge of potential associated risks is paramount and these include hypoxia, hypercapnia, inadequate depth of anaesthesia and possible accumulation of toxic trace gases.[19] The following equipment is essential for the safe practice of LFA: a leak-free circle breathing system with a carbon dioxide absorber, two unidirectional valves, a fresh gas inlet, an adjustable pressure limiting valve and a reservoir bag and patient Y-piece connection.[22] Upadya and Saneesh also list the usage of flow meters calibrated down to 50 millilitres per minute (ml/min), well-calibrated vaporisers capable of delivering high

concentrations at low FGF and minimal internal volume breathing circuits in addition to the other requirements mentioned above. [23]

Potential benefits of LFA include preservation of the patient's heat and humidity.[24-26] A 1994 study by Kleemann found that minimal FGF was the best way to improve airway climate with humidity of > 20 milligrams of water per litre (mg H_2O/l) obtained after an hour of anaesthesia. [25] These findings were confirmed in a 2017 systematic review and meta-analysis of 10 randomised controlled trials by Braz et al. [26] This improved airway humidity and temperature may result in a decrease in harmful effects of prolonged inhalation of dry gases such as impaired ciliated epithelium functioning, induction of inflammation, predisposition to atelectasis or pneumonia as well as hypothermia.[19] Other physiological advantages of LFA include conservation of body temperature, reduced dehydration and improved inhaled gas flow dynamics.[23]

There are also ecological and environmental benefits to LFA as it reduces the emission of inhalational anaesthetic gases, which deplete the ozone layer and cause greenhouse effects.[23, 27] The environmental impact of anaesthetic gases is often reported in terms of global warming potential (GWP). GWP is a measure of the radiative efficiency and atmospheric lifetime of a given mass of gas and compares it on a relative scale to the same mass of carbon dioxide (CO_2).[28, 29] Anaesthetic agents last significantly longer in the atmosphere than CO_2, as a result, the 100-year GWP is often reported. Desflurane has the longest 100-year GWP at 2540 units, followed by isoflurane at 510 units, nitrous oxide at 298 units and sevoflurane at 130 units.[10, 28, 30, 31] For a simplified perspective, an hour of anaesthesia with FGF of 0.5 – 2 L/min is equivalent to driving 18 miles (28 kilometres) in a car using sevoflurane, 20 – 40 miles (32 – 64 kilometres) with isoflurane and 235 – 470 miles (378 – 756 kilometres) with desflurane.[32] The use of nitrous oxide also significantly increases the carbon footprint of sevoflurane and isoflurane anaesthesia.[32]

Economic advantages of LFA include reduced inhalational gas consumption. In a study by Edmonds et al., an estimated US$ 96,960 was spent on sevoflurane, isoflurane and desflurane for cases in the study. [10] Using predictive simulation analysis, they found that an average FGF of 1 L/min could yield a 48% reduction in the cost of various inhalational anaesthetics used. In another study by Ryu et al., they reported savings in terms of the number of anaesthesia hours performed per bottle of sevoflurane and they saw a 38.3% increase following the implementation of policy advocating for LFA.[33]

For this study, the cost of sevoflurane will be studied as it accounts for approximately 98% of inhalational anaesthetic bottles used monthly at our institution.

4.2 Problem statement

In a resource-limited setting, there is a need for healthcare practitioners to minimise costs without compromising patient care. During inhalational anaesthesia, a cost-determining factor that anaesthesiologists have direct control over is the FGF used during anaesthesia. This average FGF is an unknown value at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH). For cost-saving strategies to be implemented, current clinical practices that drive costs must be first determined.

4.3 Aims

The study aims to prospectively analyse the conduct of inhalational anaesthesia at CMJAH in order to determine FGF and the volume of liquid agent used at different stages of anaesthesia.

4.4 Objectives

The primary objectives of the study are to:

- determine the FGF per time segment duration
- determine the inhalational agent concentration per time segment
- determine the liquid agent consumption per time segment
- determine the liquid agent expenditure per time segment.

The secondary objectives of the study are to:

- determine the average FGF used per theatre daily
- determine the average MAC during maintenance of anaesthesia
- determine the overall liquid agent consumption and expenditure per theatre daily
- determine the factors associated with the cost of sevoflurane.

4.5 Research assumptions

The following definitions will be used in the study.

Case: continuous data logs from Maquet Flow-i ® anaesthetic machines recorded at one-minute intervals. Any data entry breaks longer than ten minutes will be considered the end of a case and subsequent entries will be the start of another.

Costs: irreversible expenditure of resources to procure something or to provide a service.[34]

Fresh gas: medical oxygen/air or a mixture of the two gases used as a carrier agent during anaesthesia.[18]

Fresh Gas Flow Rate (FGF): total volume of medical gas that flows from the anaesthetic machine into the breathing system per minute.[18]

Inhalational agent: fluorinated ethers used in the operating theatre for induction and maintenance of anaesthesia. These include isoflurane, sevoflurane and desflurane.[35] For this study, this term refers to sevoflurane as it is the most widely used agent at CMJAH.

Surgery: encompasses all emergent, urgent and elective surgical procedures that are conducted.

Induction phase of anaesthesia: a period of anaesthesia from when the vaporiser is turned on until FGF drops below 5 L/min.[36]

Transition phase of anaesthesia: a period of anaesthesia from when FGF falls below 5 L/min and continues until FGF falls below 2 L/min.[36]

Maintenance phase of anaesthesia: a period of anaesthesia from when FGF falls below 2 L/min until the end of the surgery when inspired inhalational agent concentration is set to zero. Movement between phases is unidirectional and once the maintenance phase is entered, any subsequent adjustments in FGF will be considered part of the maintenance phase.[36]

Time segment: duration of anaesthesia where both the FGF and set inhalational agent concentration are constant.[37]

Inhalational agent concentration: set percentage for a vaporiser to deliver inhalational agent.

Liquid agent consumption: volume of inhalational agent used.

Liquid agent expenditure: volume of inhalational agent used multiplied by its unit cost per ml in South African Rands (ZAR).

Saturated gas volume: volume of inhalational agent vapour obtained from the evaporation of 1 ml of liquid inhalational agent.[37]

4.6 Demarcation of study field

The study will be done at the CMJAH theatre complex, which is affiliated with the University of the Witwatersrand (WITS) Faculty of Health Sciences. CMJAH is a 1200-bed quaternary hospital with 23 operating theatres and an average of 23 000 operations performed annually. Of these operating theatres, 11 have the Maquet Flow-i ® anaesthetic machines suitable for the study. The surgeries conducted in these theatres include elective and emergency cases across various disciplines.

4.7 Ethical considerations

The study will have prospective data collection of current clinical practices with no patient or anaesthesiologist identifiers included in the study. Data collected will be on set FGF rates, vaporiser settings and ambient theatre temperature, all of which cannot be traced to an individual patient or anaesthesiologist.

An application to the Human Research Ethics Committee and the Post Graduate Committee of the University of the Witwatersrand will be submitted for ethical clearance of the study before data collection. Application to the Medical Advisory Committee of the CMJAH will be submitted for approval of this study (Appendix 1).

Approval to conduct the study will be obtained from the Head of Department of WITS Anaesthesia (Appendix 2), CMJAH Department of Anaesthesiology Clinical Head (Appendix 3) and the Chief Executive Officer of CMJAH (appendix 4).

Data will be stored securely for six years after the completion of the study in a password-protected electronic database.

The study will be conducted according to the principles of the Declaration of Helsinki and the South African Guidelines for Good Clinical Practice. [38,39]

The study will be registered with the National Health Research Database.

4.8 Research methodology

4.8.1. Research design

A prospective, contextual study design will be followed. In a prospective study, the participants are followed for a period to collect data on the variable of interest as it occurs or changes.[40] This study will be prospective as data will be collected during the study period and outcomes will be measured once the study has been completed.

A contextual study refers to a specific population or place.[41] The study will be contextual as it will be undertaken at CMJAH, an academic hospital in South Africa. The outcomes cannot be generalised to the global population but rather academic institutions in peri-urban towns facing a similar patient profile, pattern of disease burden and resource availability.

4.8.2. Study population

The study population consists of data logs from Maquet Flow-i ® anaesthetic machines at CMJAH.

4.8.3. Study sample

Sample size

The study sample size was calculated using an online sample size calculator with the aid of a biostatistician.[42] It was determined that the study will consist of one cohort that will need to be compared to a known value published in previous literature, with the primary endpoint being continuous means. A study by Nair et al. [3] was selected for comparison. Their study found that the baseline FGF rate for sevoflurane at their academic hospital was 2.27±1.05 l/min. The anticipated mean for this study was estimated to be 1.9 L/min. The result was that a minimum of 105 cases will be needed for the study to have an alpha value of 0.05 and a power of 95%.

An estimated 380 cases are conducted in theatres with the Maquet Flow-i ® anaesthetic machines every two weeks. All data meeting the required inclusion criteria will continue to be collected despite reaching the minimum sample size.

Sampling method

Consecutive convenience sampling will be used for data collection. All general anaesthetic cases that meet the inclusion criteria will be included in the study.

Study period

Data will be over two weeks after all the relevant approvals are obtained. All data that meet the inclusion criteria will be included in the study.

Inclusion and Exclusion Criteria

The inclusion criteria for this study are:

- all general anaesthesia cases conducted using the Maquet Flow-i ® anaesthetic machines.
- anaesthesia conducted with closed circuit ventilation with either a laryngeal mask airway (LMA) or endotracheal tube (ETT).
- inhalational general anaesthesia of more than 45 minutes in duration
- general anaesthesia with sevoflurane.

The exclusion criteria in this study are:

- administration of more than one inhalational anaesthetic agent
- anaesthesia machines with a leak greater than 150ml/min
- usage of Auxiliary Common Gas Outlet (ACGO) during induction of anaesthesia.

4.8.4. Data Collection

At the end of each theatre day, data will be collected by plugging a USB drive into the rear USB port of Maquet Flow-i ® anaesthetic machines. The menu button will then be selected and thereafter, using the touch interface, save all data logs and trends to USB selected. This will export all data as log documents onto the connected USB drive. The saved data will be viewed on a laptop and sorted into a folder for that particular theatre. The ambient theatre temperature for the day will also be recorded. This process will be repeated for each theatre with the selected anaesthetic machine. A tally of all the cases that meet the inclusion criteria will be kept and the data collection process will be repeated daily over the two-week study period.

All data will be consolidated into a single Microsoft Excel ® spreadsheet. Each case will be identified by continuous data logs recorded at 1-minute intervals. Any data entry that breaks longer than ten minutes will be considered the end of a case and subsequent entries will be the

start of another. The different phases of anaesthesia per case will then be identified and after that, subdivided into different time segments.

Using the equations from a study by Biro, the volume of inhalational agent consumed per time segment will be calculated.[37]

$$Saturated\ Gas\ Volume\ \ (ml/ml) = \frac{specific\ weight^{1}.\ Avogadro's\ gas\ constant^{2}.(273+temperature)^{3}}{molecular\ weight^{4}.273}$$

Figure 4.8.4.1 Calculation of saturated vapour of inhalational agent. [37]

1. Specific weight of sevoflurane = 1.53 grams per millilitre (g/ml) [37]
2. Avogadro's gas constant at standard temperature and pressure = 22 400 ml [18]
3. Temperature of vaporiser = room temperature – 2 ºC due to loss of energy during evaporation [37]
4. Molecular weight of sevoflurane = 200 [37].

The calculations will account for the elevation of Johannesburg, 1760 metres above sea level[43], when calculating Avogadro's gas constant.[44] Ambient theatre temperature will be recorded daily for use in the formula. The saturated gas volume obtained using figure 4.8.4.1 will then be used in calculating fluid volatile agent consumed per time segment as shown in figure 4.8.4.2 below.

$$fluid\ volatile\ agent\ (ml) = \frac{FG\ flow\left(\frac{ml}{\min}\right).VA\ conc.(Vol\%).Anaesthesia\ duration\ (\min)}{Saturated\ gas\ volume\left(\frac{ml}{ml}\right).100(Vol\%)}$$

Figure 4.8.4.2 Biro Equation to Calculate Volume of Liquid Anaesthetic Consumed [37]

Abbreviations: FG - fresh gas; VA conc. - volatile anaesthetic concentration; Vol – volume; ml/min - millilitres per min; min – minute

The calculated volumes per time segment will then be summed up to get the total volumes per phase of anaesthesia as well as for the entire duration of the anaesthetic. To verify the accuracy of calculated volumes, they will be compared to the measured values recorded by the anaesthetic machine. The current procurement cost of sevoflurane is R813.46 per 250ml bottle or approximately R3.25/ml. This amount will then be multiplied by the total volumes of sevoflurane consumed to get the total costs.

4.8.5. Data analysis

Microsoft Excel ® will be used for data capture, thereafter, a statistical program, SPSS ®, will be used to analyse data with the consultation of a biostatistician. The descriptive results will

be presented as frequency distributions and measures of central tendency (mean, median and mode). An appropriate correlation tool will be used to determine the factors associated with the cost of sevoflurane. Overall FGF will be calculated using time-weighted means to enable comparison with other published literature. Similar to a study by Kennedy et al. the underlying data may not be normally distributed, however, this value will represent average FGF and, therefore liquid agent consumption.[36] The flow rates at different stages of anaesthesia will be described with the median and interquartile range along with the 85th centile to quantify outliers. The relationship between liquid agent consumption and mean FGF will be explored using linear regression analysis.

4.9 Significance of the study

The cost of providing healthcare services, facilities and technologies continues to rise whilst resources remain finite. As a result, healthcare practitioners need to have a cost-conscious clinical practice. With LFA, it is possible to reduce costs without compromising patient care. The significance of this study is that it will identify the baseline mean FGF and, therefore, sevoflurane liquid agent consumption at CMJAH. This will allow targeted cost-saving and quality improvement strategies to be implemented as needed.

4.10 Validity and reliability of the study

Validity is the "degree to which a measurement represents a true value". It reflects the accuracy of a measurement and there are fewer errors in the study process. Reliability refers to the reproducibility or consistency of a measurement.[45]

The following measures will ensure the validity and reliability of the study:

- an appropriate study design will be used
- a single researcher will collect all the study data
- all anaesthetic machines used will be from a single manufacturer
- all collected data will be actual measurements from the anaesthetic machines, hence highly accurate and reliable
- the data will be analysed in conjunction with a biostatistician.

4.11 Potential limitations of the study

The choice of the Maquet Flow-i ® anaesthetic machine was determined by its being the only brand of anaesthetic machine that allowed trends data to be exported onto a USB drive

without requiring any additional proprietary software or licence purchase. As a result, a possible limitation is that anaesthetists might have different FGF preferences depending on the anaesthetic machine in use. However, the positive aspect of this is improved reliability as a standard type of machine will be used.

Another possible limitation is that not all theatres are being sampled, as such, mean FGF might vary depending on the nature of the surgery performed. However, this limitation can be tested by measuring if there is a significant difference in the mean FGF of the different theatres included in the study.

4.12 Project outline

Time frame

Year	2022					2023					
Month	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	June
Proposal preparation											
Proposal submission											
Postgraduate approval											
Ethics approval											
Data collection											
Data analysis											
Article preparation											
Submission											

4.13 Financial plan

The costs will be minimal as the University of Witwatersrand's printing facilities will be used at a subsidy. All software to be used in the study is either already licensed to the university or available as open source; therefore will not have any monetary costs.

Item	Price per page	Number of pages	Copies	Total (Rands)
Proposal	1	27	10	R 270
Ethics	1	10	25	R 250
Postgraduate form	1	2	6	R 12
Final MMed submission	1	100	4	R 400
Total				R 932

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4.15 Appendices

Appendix 1: Letter to the CMJAH Medical Advisory Committee

Department of Anaesthesiology
University of the Witwatersrand

4 August 2022

To the Chairman of the Medical Advisory Committee
Charlotte Maxeke Johannesburg Academic Hospital
7 York Road, Parktown
Johannesburg
2193

Dear Sir/Madam

RE: Permission to conduct research at Charlotte Maxeke Johannesburg Academic Hospital

My name is Dr Aobakwe Setlhare and I am a registrar in the Department of Anaesthesiology. I am conducting a study as part of my Master of Medicine in Anaesthesiology titled: Sevoflurane usage and fresh gas flows in Maquet anaesthetic machines at an academic hospital.

The study aims to analyse the conduct of inhalational anaesthesia at CMJAH in order to determine the fresh gas flow and volume of liquid agent used at different stages of anaesthesia. This will aid in identifying areas of cost-containment. No personal patient information will be collected.

Ethics approval, as well as approval from the Graduate Studies Committee of the University of the Witwatersrand, will be obtained before study commencement. This study will not result in additional costs to the hospital. The results of the study will be made available to you upon request.

Yours sincerely
Dr Aobakwe Robert Setlhare
Email: aobakwest@gmail.com
Cell: 079 717 7750

Appendix 2: Letter to Head of Department WITS Anaesthesia

Department of Anaesthesiology
University of the Witwatersrand

4 August 2022

Head of Department of WITS Anaesthesia
Charlotte Maxeke Johannesburg Academic Hospital
7 York Road, Parktown
Johannesburg
2193

Dear Prof P. Motshabi

RE: Permission to conduct research at Charlotte Maxeke Johannesburg Academic Hospital

My name is Aobakwe Setlhare and I am a registrar in the Department of Anaesthesiology. I am conducting a study as part of my Master of Medicine in Anaesthesiology titled: Sevoflurane usage and fresh gas flows in Maquet anaesthetic machines at an academic hospital.

The study aims to analyse the conduct of inhalational anaesthesia at CMJAH in order to determine the fresh gas flow and volume of liquid agent used at different stages of anaesthesia. This will aid in identifying areas of cost-containment. No personal patient information will be collected.

Ethics approval, as well as approval from the Graduate Studies Committee of the University of the Witwatersrand, will be obtained before study commencement. There will be no financial implications to the department and a copy of the final report will be made available to you upon request.

Yours sincerely

Dr Aobakwe Robert Setlhare
Email: aobakwest@gmail.com
Cell: 079 717 7750

Appendix 3: Letter to HOD of the Department of Anaesthesiology at CMJAH

Department of Anaesthesiology
University of the Witwatersrand

4 August 2022

Head of Department of Anaesthesiology
Charlotte Maxeke Johannesburg Academic Hospital
7 York Road, Parktown
Johannesburg
2193

Dear Prof E.E. Oosthuizen

RE: Permission to conduct research at Charlotte Maxeke Johannesburg Academic Hospital

My name is Aobakwe Setlhare and I am a registrar in the Department of Anaesthesiology. I am conducting a study as part of my Master of Medicine in Anaesthesiology titled: Sevoflurane usage and fresh gas flows in Maquet anaesthetic machines at an academic hospital.

The study aims to analyse the conduct of inhalational anaesthesia at CMJAH in order to determine the fresh gas flow and volume of liquid agent used at different stages of anaesthesia. This will aid in identifying areas of cost-containment. No personal patient information will be collected.

Ethics approval, as well as approval from the Graduate Studies Committee of the University of the Witwatersrand, will be obtained before study commencement. There will be no financial implications to the department and a copy of the final report will be made available to you upon request.

Yours sincerely,

Dr Aobakwe Robert Setlhare
Email: aobakwest@gmail.com
Cell: 079 717 7750

Appendix 4: Letter to Chief Executive Officer of CMJAH

Department of Anaesthesiology
University of the Witwatersrand

4 August 2022

Chief Executive Officer
Charlotte Maxeke Johannesburg Academic Hospital
7 York Road, Parktown
Johannesburg
2193

Dear Sir/Madam

RE: Permission to conduct research at Charlotte Maxeke Johannesburg Academic Hospital

My name is Aobakwe Setlhare and I am a registrar in the Department of Anaesthesiology. I am conducting a study as part of my Master of Medicine in Anaesthesiology titled: Sevoflurane usage and fresh gas flows in Maquet anaesthetic machines at an academic hospital.

The study aims to analyse the conduct of inhalational anaesthesia at CMJAH in order to determine the fresh gas flow and volume of liquid agent used at different stages of anaesthesia. This will aid in identifying areas of cost-containment. No personal patient information will be collected.

Ethics approval, as well as approval from the Graduate Studies Committee of the University of the Witwatersrand, will be obtained before study commencement. There will be no financial implications to the department and a copy of the final report will be made available to you upon request.

Yours sincerely,

Dr Aobakwe Robert Setlhare
Email: aobakwest@gmail.com
Cell: 079 717 7750

Appendix 5: Data collection sheet

Case ID: 1	Theatre:	Case Duration (min):	Ambient temp (°C):	
Time	Fresh gas flow (L/min)	Vaporiser setting (%)	MAC	Volume per time segment
08:00				
08:01				
08:02				
…….				

Section 5: Annexures

5.1 Human research ethics committee clearance certificate

M230147 MED22-12-019

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Aobakwe Robert Setlhare

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M230147 MED22-12-019

NAME: (Principal Investigator)	Dr Aobakwe Robert Setlhare
DEPARTMENT:	Anaesthesia Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	Sevoflurane usage and fresh gas flows in Maquet anaesthetic machines at an academic hospital
DATE CONSIDERED:	27/01/2023
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr K Pegu, Dr M Sehlapelo and Dr H Moutlana
APPROVED BY:	Dr C Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	03/04/2023 **EXPIRY DATE:** 03/04/2028

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report** in January each year until study is closed. Failure to submit annual report will result in ethics clearance certificate suspension. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed January and will therefore be due in the month of January each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical). Login to upload signed copy of this ethics clearance certificate prior to commencing with the study
https://www.witsethics.co.za/login.aspx

Principal Investigator Signature

12 April 2023
Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

5.2 Graduate studies committee approval

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

06 January 2023
Person No: 2620669
PAG

Dr AR Setlhare
Unit 642 The Polofields
Polofields Drive
Waterfall
2090
South Africa

Dear Dr Aobakwe Setlhare

Master of Medicine in Anaesthesia: Approval of Title

We have pleasure in advising that your proposal entitled *Sevoflurane usage and fresh gas flows in Maquet anaesthetic machines at an academichospital* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

5.3 Charlotte Maxeke Johannesburg Academic Hospital CEO Approval

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG
ACADEMIC HOSPITAL
OFFICE OF THE CLINICAL DIRECTOR

Enquiries: *Ms N. Mzila*
Email: Nolwazi.Mzila@gauteng.gov.za
Tel: *011 488 3365*
Ref: *1/7/2*
Date: 25 April 2023

GP_202303_027

DEAR DR AOBAKWE ROBERT SETLHARE

RE: FINAL APPROVAL OF STUDY

TITLE: SEVOFLURANE USAGE AND FRESH GAS FLOWS IN MAQUE ANAESTHETIC MACHINES AT AN ACADEMIC HOSPITAL

Permission is granted for you to conduct the above-mentioned study as described in your request provided:

1. Charlotte Maxeke Johannesburg Academic Hospital will not in any way incur or inherit costs as a result of the said study.
2. Your study shall not disrupt services at the study sites.
3. Strict confidentiality shall always be observed.
4. Informed consent shall be solicited from patients participating in your study.

Please liaise with the HOD and Unit Manager or Sister in charge to agree on the dates and time that would suit all parties.

Kindly forward this office with the results of your study on completion of the research.

Supported / ~~Not Supported~~

Signed by:Jayshina Punwasi
Signed at:2023-04-26 23:38:39 +02:00
Reason:Witnessing Jayshina Punwasi

Dr J. Punwasi
Clinical Director

Approved / ~~Not Approved~~

Signed by:Gladys Magugudi Bogoshi
Signed at:2023-04-27 06:43:12 +02:00
Reason:Witnessing Gladys Magugudi Bo

Ms G. Bogoshi
Chief Executive Officer: CMJAH

5.4 Permission letter by the WITS Anaesthesiology Head of Department

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG | FACULTY OF HEALTH SCIENCES | WITS SCHOOL OF CLINICAL MEDICINE | DEPARTMENT OF ANAESTHESIOLOGY
Tel.(011)488 4344

02 March 2023

Postgrad Office

School of Clinical Medicine

Faculty of Health Sciences

University of the Witwatersrand

To Whom It May Concern

Permission To Conduct Research: Dr Aobakwe Robert Setlhare Student number 2620669

This is to confirm that I have read and given permission for Dr Aobakwe Robert Setlhare to conduct research at in the Department of Anaesthesiology towards his/her Mmed project titled **"Sevoflurane usage and fresh gas flows in Maquet anaesthetic machines at an academic hospital"**

Thank you.

Assoc. Prof. P Motshabi Chakane

Ass Prof P. Motshabi Chakane
HOD Wits Anaesthesia
HOU Cardiac Anaesthesia
Tel: +27 (0)11 488 4344
Cell: 083 432 1994
Email: palesa.motshabi@wits.ac.za
Website: www.wits.ac.za
Charlotte Maxeke Johannesburg Academic Hospital, 6th Floor, Area 361/16, Jubilee Road, Parktown, Johannesburg

5.5 Permission letter by the CMJAH Anaesthesiology Head of Department

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

DEPARTMENT OF ANAESTHESIA
Area 361
Charlotte Maxeke Johannesburg Academic Hospital

Tel: 011 488 4344
Fax: 086 765 3477

2 March 2023

Dr AR Setlhare
Registrar: Department of Anaesthesia

Dear Dr Setlhare

APPROVAL FOR MMed RESEARCH DATA COLLECTION

I fully support the participation of the Department of Anaesthesia at CMJAH in your MMed research study, titled: *"Sevoflurane usage and fresh gas flows in Maquet anaesthetic machines at an academic hospital."* The findings from this study has the potential to contribute towards improved cost effectivity in our operating theatres.

The departmental support for this study is subject to the usual preconditions, namely that the study has no cost implications to the department and hospital. Additionally, the research proposal must be approved by all the relevant authorities, including ethics and research committees, before data collection can start.

Yours sincerely,

Prof EE Oosthuizen
Clinical head: Department of Anaesthesia
Charlotte Maxeke Johannesburg Academic Hospital

5.6 Turnitin report

2620669 - Setlhare MMED Turnitin Report-a8d7b7ed-96fa-4ff2-833e-d7f09bab097b.pdf

ORIGINALITY REPORT

12%	9%	7%	4%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	archive.org Internet Source	1%
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3	www.ajol.info Internet Source	1%
4	R. R. Kennedy, R. A. French, G. Vesto, J. Hanrahan, J. Page. "The effect of fresh gas flow during induction of anaesthesia on sevoflurane usage: a quality improvement study", Anaesthesia, 2019 Publication	1%
5	Submitted to University of Stirling Student Paper	1%
6	Hosur, Veeresh. "Efficacy of Bispectral Index (BIS) Monitoring on Sevoflurane Consumption and Postoperative Recovery Among Patients Undergoing Laparoscopic Surgeries", Rajiv	1%

5.7 Turnitin supervisor's report

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

15 March 2024

The Chairperson

Graduate Studies Committee

Faculty of Health Sciences

University of the Witwatersrand

Dear Madam,

RE: M Med: **Sevoflurane usage and fresh gas flows in Maquet anaesthetic machines at an academi hospital**

Dr Aobakwe Robert Setlhare, student number: 2620669, has submitted his research report to Turnitin which revealed a similarity index of 12%. These similarities appear not to be plagiarism but mainly the use of common terminology and phrases specific to the topic of the research.

Yours sincerely,

Mathabe Sehlapelo

Supervisor