A Randomised Control Trial to Compare Quality of Recovery between Desflurane and Isoflurane Inhalational Anaesthesia in Patients Receiving General Anaesthesia for Ophthalmological Surgery at Dr. George Mukhari Academic Hospital

(DIQoR Trial)

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Issue Date: 8 April 2019
Protocol Amendment Number: 2
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1 Administrative Information

1.1 Trial Registration

1.1.1 Registry
To be registered in ClinicalTrials.gov after approval by School Research Committee and SMU Research Ethics Committee.

1.1.2 WHO Data Set
To be completed once registration has been done.

1.2 Revision Chronology

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<td>Amendments after first review by SMU School Research Committee, formatted according to SPIRIT Statement 2013. Change in title and development of acronym.</td>
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1.3 Roles and Responsibilities
CS conceived of the study and wrote the protocol. HK acted as supervisor and guided the process.

CS will be responsible for obtaining funding through research grants.

CS will be responsible for the overall conducting of the trial: including recruitment, training and liaising with treating anaesthetists and the research assistant, data collection and analysis and writing up the trial for publication.

1.4 Funding

- Expenses = R 51 037:
  - Statistician fee (including: data plan, data analysis and randomisation service): R 5 000
  - Desflurane (6 bottles): R 9 537 (incl. VAT)
  - Translation costs: R 3 500
  - Printing costs: R 3 000
  - Research assistant: a research assistant will be paid R100 per hour to visit the patient post-operatively in order to complete the QoR, as well as to read the data into REDCap.
    - Estimated 2 hours per day, 25 days per month, for 6 months = R30 000
• Income:
  o Abbvie Scholarship: R 10 000
    ▪ The chief researcher is a current recipient of the Abbvie Scholarship.
  o JPRF application: R50 000
    ▪ Once ethical approval has been obtained, the chief researcher will apply for funding from the SASA Jan Pretorius Research Fund. (Grants are made to deserving members of SASA for clearly defined research projects, which are acceptable to SASA and fall within the scope of Anaesthesia.)

1.5 Timeline

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<td>April 2019</td>
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<td>Middle September 2019</td>
<td>Review results of pilot study</td>
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<td>Jan 2020</td>
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<tr>
<td>July / August 2020</td>
<td>End Data Collection</td>
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<tr>
<td>September 2020</td>
<td>Data analysis</td>
</tr>
<tr>
<td>October 2020</td>
<td>Write dissertation and research article</td>
</tr>
<tr>
<td>December 2020</td>
<td>Submit dissertation for evaluation and submit article for publication</td>
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2 Introduction

2.1 Background

2.1.1 Study Problem and Research Question

Recovery after surgery and anaesthesia has traditionally been assessed with objective measures including time to awakening, time to regaining airway reflexes, duration of stay in the recovery room and/or hospital, and incidence of adverse events like pain and post-operative nausea and vomiting. Increasingly, the patient’s experience of their post-operative recovery is being recognised as an important outcome after surgery. The 15-Item Quality of Recovery score (QoR-15) has been validated to give a patient-centred global measure of overall health status after surgery and anaesthesia (1,2). This score has recently been translated and validated in isiZulu (3).
Desflurane is the newest anaesthetic vapour to market, with many benefits from the anaesthetist's perspective: faster time to awakening, faster time to regaining airway reflexes, and a clearer sensorium post-operatively. However, there is a paucity of data evaluating whether this translates to better quality of recovery for the patient. Desflurane is more expensive than other volatiles; for economic use, it is recommended to use Desflurane with a low flow (up to 2L) anaesthetic technique. Concerns have also been raised about the environmental impact of using Desflurane, because the molecule persists in the atmosphere for 14 years, and it has a high Global Warming Potential (GWP) (4).

Isoflurane is the most commonly used volatile anaesthetic agent at Dr. George Mukhari Academic Hospital. Concerns about the increased cost of desflurane compared to isoflurane limits the use of this novel agent in the public sector in South Africa. Following an extensive literature review, no studies could be found comparing quality of recovery between desflurane and isoflurane using a validated quality of recovery tool like the QoR-15.

The research question in this study is whether there is a clinically significant difference in post-operative quality of recovery (using the QoR-15 score) between desflurane and isoflurane inhalational anaesthesia in adult patients presenting for elective ophthalmological surgery under general anaesthesia.

This study will therefore compare quality of recovery between desflurane and isoflurane inhalational anaesthesia. Furthermore, the study will evaluate the relative cost of using either volatile with a basal flow anaesthetic technique.

2.1.2 Literature Review

The ideal volatile anaesthetic should be potent, with a low solubility in blood and tissues, which should promote fast onset and offset of the drug effect. It should provide safe, effective and reliable anaesthesia with minimal side-effects. The agent must be able to resist physical and metabolic degradation, and it should not pose a threat to the environment (5). Preferably, it should also be cost-effective and simple to use. One aspect that is often overlooked in the description of the “ideal anaesthetic agent”, is the quality of recovery from the patient’s point-of-view.

Isoflurane is the most commonly used inhaled anaesthetic agent at Dr. George Mukhari Academic Hospital. Desflurane has recently become available. Both agents are indicated for maintenance of anaesthesia. Neither agent is indicated for induction of anaesthesia, as they are pungent and irritating to the airways.

The side-effect profiles of the two vapours are similar. Both agents may cause respiratory irritation (coughing, bronchospasm, laryngospasm) and respiratory depression. Both agents may cause myocardial depression and hypotension in a dose-dependent fashion. Desflurane may cause a transient, indirect stimulation of the sympathetic nervous system which may arise from stimulation of rapidly adapting upper airway receptors.
Isoflurane may also cause emergence reactions, cardiac arrhythmias, involuntary muscle movements and hiccupping. Both agents may cause post-operative shivering, nausea and vomiting, as well as leucocytosis (even in the absence of surgical stress). Both agents may interact with carbon dioxide adsorbents to form carbon monoxide, especially when the adsorbent dries out; carbon monoxide inhalation may lead to formation of carboxyhaemoglobin in exposed patients (6–8).

Both Isoflurane and Desflurane are contra-indicated in patients who may be susceptible to Malignant Hyperthermia or to auto-immune hepatitis. Isoflurane should be avoided in patients with cerebral space occupying lesions or raised intracranial pressure. Both agents will be contra-indicated when general anaesthesia is contra-indicated.

There have been concerns in the anaesthetic community about the environmental impact of Desflurane (4,9–11). All the halogenated anaesthetic vapours are greenhouse gases. The greenhouse effect stems from the infrared absorptive capacity of these gases when released into the atmosphere. Incoming solar radiation to the Earth is mostly reflected outwards as infrared radiation at a peak frequency of 10 micrometres. Halogenated anaesthetic agents absorb infrared radiation within the range of 7-10 micrometres – thereby preventing outwards reflection of infrared radiation, and contributing to the increase in the Earth’s temperature. The global warming potential (GWP) of a greenhouse gas is estimated over a 100 year period (the atmospheric lifetime of CO2). The GWP depends on the lifetime of the greenhouse gas, as well as it’s radiative frequency. Desflurane persists in the atmosphere for 14 years, and has a GWP100 of 2540. By convention, the GWP100 of CO2 is 1. Vaporising a 240ml bottle of Desflurane releases the equivalent of 893kg of CO2 (11). In comparison, vaporising a 250ml bottle of Isoflurane releases 190kg CO2e and vaporising a 250ml bottle of Sevoflurane releases 49kg CO2e. Isoflurane persists in the atmosphere for 3.2 years, and Sevoflurane for 1.1 years. The GWP100 for Isoflurane and Sevoflurane are 510 and 130, respectively. (4,12).

As a result of the environmental concerns, there are movements in the UK to reduce the use of inhaled anaesthetic agents as a whole, and Desflurane in particular (11,13,14). However, all inhaled anaesthetics released during all anaesthetic procedures globally have an impact of only about 0.01% of that of all the CO2 released from global fossil fuel combustion (4). An estimated 960 tonnes of Desflurane is released into the atmosphere annually, compared to 37.1 gigatonnes of CO2 that is released globally per year (15,16). CO2 emissions from global health care are estimated to be about 2 gigatonnes per year. 71% of health care emissions come from the health care supply chain (production, transport, use and disposal). 17% of health care emissions are directly from health care facilities, and 12% of health care emissions are from indirect sources like electricity, steam, cooling and heating. Anaesthetic vapour related emissions contribute to direct health care emissions. (17) Though it is important to limit
greenhouse gas emissions, focussing on reducing the relatively small impact of anaesthetic vapours like Desflurane, is unlikely to make a dramatic difference to the environmental impact of the health care industry. (4)

“Recovery” and “Quality of Recovery” are complex, abstract concepts, lacking in universally accepted definitions. In basic terms, “Recovery” can be seen as a return to the patient’s pre-operative state, or indeed, to an improved state. This is dependent on patient, surgical and anaesthetic factors. “Quality of Recovery” is a patient-centred concept, and several valid and reliable instruments have been developed that take into account physical and mental well-being factors that impact on the patient’s experience of their recovery (18).

Quality of recovery should be distinguished from patient satisfaction. Whether quality of recovery has an impact on patient satisfaction is unclear (19). Patient expectations, cultural and social background and cognitive factors all impact on patient satisfaction. Tools evaluating patient satisfaction emphasise the following: information provided to the patient, physical comfort, involvement in care, emotional support and privacy (18).

Recovery after inhaled anaesthesia has mostly been evaluated by parameters related to speed of emergence from anaesthesia, for example: time to open eyes, time to respond to command, time to remove LMA, and time to state date of birth. For all of these parameters, the time to effect is significantly shorter for desflurane compared to sevoflurane, isoflurane and propofol (5,20,21).

Some studies have evaluated later end-points of recovery including level of activity and side-effects on the day after surgery. Mahmoud et al (22) evaluated female patients who underwent laparoscopic gynaecological day-case surgery with either sevoflurane or desflurane for maintenance of anaesthesia; they found that the patients who received desflurane had greater return to normal activity the day after surgery compared to the sevoflurane group. This was done using a semi-structured telephonic questionnaire. White et al (23) found no difference in later end-points of recovery between sevoflurane and desflurane in patients undergoing superficial surgical procedures. This was assessed with a telephonic interview the day after surgery. This trial also included a basic assessment of patient satisfaction with their anaesthetic experience on a 3-point rating scale: 0 = dissatisfied, 1 = satisfied and 2 = highly satisfied. There was no difference in satisfaction between the two groups.

Studies comparing desflurane and isoflurane have been done, most also focussing on parameters relating to emergence from anaesthesia, as stated above. Emergence has been found to be faster for patients receiving desflurane; a finding that holds true for obese and elderly patients (5). Many of the early studies aimed for alveolar concentrations in excess of 1x the minimum alveolar concentration (MAC) of the volatile agents, which may explain the greater incidence of adverse reactions seen with desflurane. Jakobsson et al (24) compared desflurane and isoflurane anaesthesia in patients undergoing laparoscopic gynaecological surgery. Their study confirmed shorter
time to emergence with desflurane, including time to extubation and return of cognitive function, and similar rates of post-operative nausea and vomiting and pain. Patients were asked to rate the quality of anaesthesia as “good – better than expected” or “bad – worse than expected”. There was no significant difference between the two groups.

A systematic review published in 2004 comparing the recovery profiles after ambulatory anaesthesia with propofol, isoflurane, sevoflurane and desflurane, included 4 studies comparing desflurane and isoflurane. Unfortunately, none of the studies included in the review reported on later end-points of recovery or quality of recovery (25).

Few studies comparing volatile anaesthetic agents used validated quality of recovery tools. One study, reported in German in 2011, used the QoR-40 at 24 hours to evaluate differences between anaesthesia with desflurane and sevoflurane. Though parameters for early postanaesthetic recovery were superior in the patients receiving desflurane, there was no difference in the QoR-40 after 24 hours (26). A recently published randomised controlled trial primarily evaluating the effects of desflurane, sevoflurane and propofol on emergence times and airway reactions, evaluated patient responses to the Post-operative Quality of Recovery Score (PQRS) as a secondary outcome, and found no difference in quality of recovery between the groups (21).

Numerous tools have been developed in recent years to evaluate the quality of recovery from the patient's perspective (18). Multi-dimensional scales like the 24h Functional Ability Questionnaire (24h-FAQ), Postoperative Recovery Profile, Postoperative Quality of Recovery Scale (PQRS), Functional Recovery Index (FRI), and the 40-Item and 15-Item Quality of Recovery Scores (QoR-40 and QoR-15) have demonstrated comprehensive postoperative outcome results. The recent systematic review by the StEP-COMPAC group (Standardized Endpoints for Perioperative Medicine, Core Outcomes Measures in Perioperative and Anaesthetic Care) recommended one or more of six defined end-points be used in clinical trials assessing patient comfort after surgery (27). The QoR-15 is included in this list of six end-points: pain intensity at 24 h postoperatively, nausea and vomiting, one of two quality-of-recovery (QoR) scales (QoR score or QoR-15), time to gastrointestinal recovery, time to mobilisation, and sleep quality. The systematic review by Kleif et al (2) also recommends that the QoR-15 be used as a standard measure of quality of recovery in clinical trials in surgery and anaesthesia.

Previously, the QoR-40 was recommended as a global measure to assess the patient's experience of their overall health status after surgery and anaesthesia, but it takes around 10 minutes to complete. The QoR-15 was developed as an abbreviated version of the QoR-40, that would be more feasible in research and clinical practice; this questionnaire can be completed in less than 3 minutes (1).
The QoR-15 is a 15-item post-operative score evaluating both physical and mental well-being by assessing five dimensions: emotional state, physical comfort, psychological support, physical independence and pain. Each of the 15 items are scored by the patient from 0 (worst score) to 10 (best score), giving a lowest possible score of 0, and a highest possible score of 150. This continuous composite score allows comparisons between intervention groups. The minimal clinically important difference (MCID) and patient acceptable symptom state score for the QoR-15 score has been determined: the MCID is 8 and the acceptable symptom state score is 118 (28). The QoR-15 has good scaling properties, and during development and testing the scores followed a normal distribution (1).

The QoR-15 has undergone extensive validation and psychometric evaluation. The English and translated versions have been found to have good validity and reliability in assessing quality of recovery (2). During development and testing, the QoR-15 was able to discriminate between men and women. This is important as it has previously been shown that women generally have a worse post-operative experience. The QoR-15 furthermore showed a negative correlation with duration of surgery, duration of time spent in the post-anaesthesia care unit, and duration of hospital stay (1).

During an extensive review of the literature, no studies could be found comparing quality of recovery between desflurane and isoflurane using a validated quality of recovery tool like the QoR-15. Isoflurane is the most commonly used volatile anaesthetic agent at Dr. George Mukhari Academic Hospital. Desflurane is being introduced into our practice, and it remains to be seen if it holds benefits with regards to patient-rated quality of recovery.

2.2 Aim and Objectives

2.2.1 Aim

This study will compare quality of recovery between desflurane and isoflurane inhalational anaesthesia.

2.2.2 Primary Objective and Hypothesis

The primary objective of the study is to evaluate whether there is a difference between post-operative quality of recovery in patients who received desflurane and in patients who received isoflurane for maintenance of anaesthesia, using the QoR-15 score, a patient-rated outcome measure.

Isoflurane is the standard drug used in our setting for maintenance of anaesthesia and will therefore be used as the drug for the control group. Desflurane will be used as the interventional drug.

The minimal clinically important difference for the post-operative QoR-15 has been found to be 8. In other words, an intervention that changes the mean post-operative score by 8, can be interpreted to signify a clinically important improvement or deterioration.
The null hypothesis for this study is that there is no statistically significant difference in mean post-operative QoR-15 scores of patients receiving isoflurane and desflurane for maintenance of anaesthesia. The alternative hypothesis is that there is a statistically significant difference in mean post-operative QoR-15 scores between patients receiving isoflurane and desflurane.

2.2.3 Secondary Objectives

A secondary objective will be to compare the consumption and relative cost of using isoflurane vs desflurane with a basal flow anaesthetic technique. This will be done by comparing the amount of vapour used in millilitre per hour between desflurane and isoflurane during basal flow anaesthesia. The relative cost of the vapour used will be estimated, based on the current government purchase price of isoflurane and desflurane.

Furthermore, the difference in time spent in recovery between the two patient groups will also be compared.

3 Methodology

3.1 Trial Design

This study will be conducted as a randomised, controlled, patient and observer blinded, single-centre trial with two parallel groups and a primary end-point of 15-point Quality of Recovery Score on day 1 after surgery. Randomization will be performed as block randomization with a 1:1 allocation.

3.2 Participants, Interventions and Outcomes

3.2.1 Study Setting

The study will be conducted in the theatre complex at Dr. George Mukhari Academic Hospital, a tertiary training centre affiliated with Sefako Makgatho Health Sciences University. Specifically, the study will be conducted in the ophthalmological theatre, on patients undergoing ophthalmological surgery under general anaesthetic.

The decision to use patients for ophthalmological surgery is based on the consideration that the procedures last an average of 1 hour, the patients are usually systemically well, the anaesthetic technique can be standardised for all patients, the surgery itself is unlikely to lead to poor quality of recovery and the patients are unlikely to require high doses of opioids for analgesia. Review of the theatre records for the ophthalmology theatre revealed that 166 patients between the ages of 18-87 years underwent general anaesthesia in the 6 months between 1 March – 31 August 2018. Mean age was 42 years, with 150 patients in the age range 18-65 years. Mean duration of surgery was 74 minutes (range: 20-180 minutes), with 141 cases lasting 40-120 minutes.

3.2.2 Eligibility Criteria

Inclusion Criteria:

- Adult patients between the ages of 18-80 years of age.
• Patients presenting for ophthalmological surgery under general anaesthesia.
• ASA I and II.
• Literate in English, Setswana or Afrikaans.

Exclusion Criteria:
• Patients outside the specified age range.
• ASA III and above.
• Patients with contra-indications to Laryngeal Mask Airway use during general anaesthesia.
• Patients with severe medical or surgical conditions, who are expected to have prolonged admissions or ICU admissions.
• Patients with uncontrolled psychiatric conditions like depression, schizophrenia, mania, dementia.
• Patients with known allergy or adverse reaction to volatile anaesthetics.
• Patients with known or suspected susceptibility to Malignant Hyperthermia.
• Patients with incomplete records (Data Collection Form and QoR-15).

3.2.3 Interventions
The control group will receive isoflurane for maintenance of anaesthesia. The intervention group will receive desflurane for maintenance of anaesthesia.

Standard protocols for induction and maintenance of anaesthesia will be followed, as discussed with Prof. F. Puehringer, an international expert in the field of desflurane use. A detailed leaflet describing the protocol has been developed (see Appendix 6.4), which will be handed to the treating anaesthetist on the day of surgery.

• Intravenous Induction of Anaesthesia:
  o Fentanyl 3 mcg/kg pre-induction to reduce airway responses during manipulation.
  o Lignocaine 40 mg pre-induction to minimize Propofol-induced injection pain.
  o Propofol 2 mg/kg until induction of anaesthesia.
  o Dexamethasone 8mg after induction of anaesthesia to prevent post-operative nausea and vomiting and to decrease opioid requirements.
  o Mask ventilation with 6 l/min 100% oxygen until airway is placed.
  o Airway management will be with a Laryngeal Mask Airway (LMA), size selected according to patient weight.

• Maintenance of Anaesthesia:
Isoflurane: After the airway is secured, fresh gas flow is reduced to 2 l/min and the Isoflurane vaporiser is opened and adjusted to attain 1MAC. Once 1MAC is attained, the fresh gas flow will be reduced to 0.2 l/min 100% oxygen and the vaporiser will be adjusted to maintain 1MAC.

Desflurane: After the airway is secured, fresh gas flow is reduced to 2 l/min and the desflurane vaporiser is opened to 12%. This is maintained until 1MAC is reached. The fresh gas flow will then be turned down to 0.2 l/min 100% oxygen and the vaporiser adjusted to maintain 1MAC.

The use of basal fresh gas flow is intentional, to minimise the amount of anaesthetic vapour used. When basal flow is used, 100% oxygen is required to meet oxygen demand.

Managing Potential Problems:

- Should the bag on the anaesthetic machine collapse during basal flow anaesthesia (e.g. because of a poor seal from the LMA, the bag may be re-inflated by pushing the Oxygen Flush button. Vapour flow should be adjusted to maintain 1MAC.
- Should the ophthalmologist complain that the patient is in too light a plane of anaesthesia, the patient may be deepened with a bolus of Propofol 0.5-1 mg/kg.
- For intra-operative analgesia (for example if patient develops tachycardia or hypertension), administer 50mcg Fentanyl boluses intravenously.
- For post-operative analgesia (only if required), administer 50-100mg of Tramadol intravenously as a bolus.
- For post-operative nausea or vomiting (only if required), administer 4mg of Ondansetron intravenously as a bolus, followed by 10mg of Metoclopramide after 30 minutes (only if further treatment is required).

Wash-out of volatile anaesthetic:

- At the end of the procedure, the vaporisers will be closed, and fresh gas flow will be increased to 6 l/min in order to wash out the volatile anaesthetic.

Recovery and Discharge

- The patient will be taken to the recovery room when they are able to protect their airway, as per normal practice.
- Discharge from the recovery room to the ward will be according to the standard procedures in the post-anaesthesia recovery room. Patients should score at least 9 on the modified Aldrete score, with the patient awake and alert with stable vital signs, not experiencing any acute side effects (e.g., nausea or vomiting) or moderate-to-severe pain.
3.2.4 Materials, Apparatus and Instruments

Basic Materials and Apparatus:

- Patients will be induced in the ophthalmology theatre; anaesthesia will be maintained with the Dräger Perseus anaesthetic work station.
- Isoflurane is freely available, and the standard anaesthetic vapour that is used in our setting.
- Desflurane will be purchased for use in the study.
- Vaporisers for both isoflurane and desflurane are available in our theatre complex.
- Nitrous Oxide will not be used as part of the fresh gas mixture, because it is not always available in our setting.
- Standard monitors will be used during anaesthesia: non-invasive blood pressure monitoring, pulse oximetry, 3-lead electrocardiogram, capnography and gas analysis.

Instruments:

Quality of Recovery will be measured with the 15-Item Quality of Recovery score (QoR-15):

- The English version can be used for English-speaking patients. There is no copyright on the form (confirmed by the author, Prof. P.S. Myles via email).
- The form will be translated into Afrikaans and Setswana.
  - Forward translation has been done in advance by an accredited medical translator at Zwelinhle Translation Services (See Appendices 6.8 and 6.9).
  - Back translation of either translation will be done by a separate panel of health care professionals, who are blinded to the original English version.
  - The final versions will be corrected and adapted by all panel members.
- The QoR-15 is a validated and reliable tool for measuring quality of recovery. The patient is asked to rate their experience of 15 items from 0 (worst score) to 10 (best score).

3.2.5 Feasibility

Consensus on the acceptability feasibility of the treatment protocol will be obtained from peers and colleagues in the Department of Anaesthesia by circulating the proposed standardised treatment protocol (see Appendix 6.4) and asking for feedback. Feedback will be recorded and reviewed by the Chief Researcher (see Appendix 6.2). It is possible that some colleagues may be hesitant to use a novel drug that they have no or minimal experience with. If there is widespread concerns around acceptability among colleagues, a training session explaining how to use Desflurane will be held as part of the departmental academic program. If less than 10 colleagues raise concern, individual training sessions will be held.
Practicality feasibility of the standardised anaesthesia treatment protocol will be tested in a pilot of 4 cases. The cases for the pilot will not be randomised and will not be included in the study data. Isoflurane will be used for 2 cases and desflurane will be used for 2 cases. The standardised anaesthesia treatment protocol describes how the anaesthetic should be conducted and it makes provision for managing eventualities like intra-operative pain, too light a plane of anaesthesia and post-operative pain and nausea. It is unlikely that large scale changes will have to be made to the standardised treatment protocol, but dose adjustments will be made if required, for example to manage the depth of anaesthesia. If it is found that the treating anaesthetists struggle with implementing the standardised protocol, a further training session will be held in the department.

Evaluating the acceptability and practicality feasibility and managing the outcomes will improve adherence to the study protocol.

3.2.6 Outcomes

Primary outcome measures:

- Quality of recovery will be assessed in all participants with the QoR-15 score.
  - A baseline QoR-15 will be measured pre-operatively, and a repeat measurement will be done on day 1 post-operatively before discharge.
  - For each patient, the pre- and post-operative QoR-15 scores will be recorded, as well as the difference between the two measurements. The mean and median differences between the pre- and post-operative QoR-15 scores of the control group and the intervention group will be compared and tested for significance.
  - The mean and median post-operative QoR-15 scores of the control group and the intervention group will be compared and tested for significance.

Secondary outcome measures:

- To evaluate the consumption and cost of isoflurane and desflurane with a basal anaesthetic technique:
  - The vapour use per case in millilitres will be recorded from the anaesthetic machine.
  - The purchase price for isoflurane and desflurane will be obtained from the pharmacy.
  - The mean and median consumption of vapour between the two groups will be compared.
  - The mean and median cost of isoflurane and desflurane will be compared.

- To evaluate time in recovery:
  - The time the patient enters and leaves the recovery room will be recorded, as well as the total time the patient spends in the recovery room.
  - The mean and median time spent in recovery will be compared between the two groups.
### 3.2.7 Participant Timeline and Flow-Diagram

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ENROLLMENT

Pre-Operative Day -1

Chief Researcher reviews theatre list

1. Identify adult patients between 18-80 for general anaesthesia
2. Review patients in the ward. Assess for eligibility.

Review information leaflet with patient
Complete the following documents:
• Consent form
• Data Collection Form Section A
• Pre-operative QoR-15 score

Exclude when:
• Not meeting all inclusion criteria
• Meeting any of exclusion criteria
• Patient declines to participate

Allocation

Operative Day 0

Randomisation

Allocated to Control Group (Isoflurane treatment protocol) Target n = 85
Allocated to Intervention Group (Desflurane treatment protocol) Target n = 85

Procedure

Operative Day 0

Treating anaesthetist completes the following documents:
• Data Collection Form Section B
Completed form handed back to Chief Researcher

Follow-up

Post-Operative Day 1

Research assistant visits patient post-operatively.
Complete the following documents:
• Post-operative QoR-15 score
Data entered into REDCap.
Patient discharged by surgeon.

Analysis

Once Data Collection Completed

Statistical analysis of all data.
Exclude cases with incomplete study documents.

C. Steyl. Student Nr: 201710494

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3.2.8 Sample Size

Sample size calculation is based on estimation of the difference in mean post-operative Quality of Recovery (QoR) scores, after anaesthesia with desflurane or isoflurane. With a sample size of 85 in each group, a two-sided two-sample t-test at the 5% significance level, will have 80% power to detect a difference of 8 between the mean post-operative QoR scores with desflurane and isoflurane, assuming a standard deviation of 18.5. Sample size calculation was done on nQuery Advanced (Statistical Solutions Ltd, Cork, Ireland), Release 8.0.

A sample of 170, randomised in a 1:1 ratio to treatment with desflurane and isoflurane (85 per group) is proposed for this study.

3.2.9 Recruitment

Recruitment will be done by the Chief Investigator. The following steps will be followed:

1. Review the theatre booking list for theatre 11 the day before surgery.
2. Identify adult patients between the ages of 18 and 80 on the list, scheduled for general anaesthesia.
3. Review the patients in the ward:
   a. Screen for any exclusion criteria.
4. Once confirmed that there are no exclusion criteria:
   a. Explain the objectives of the study to the patient.
   b. Hand the patient a patient information leaflet and discuss any questions the patient may have.
   c. Take informed consent if the patient agrees to participate in the study.
5. Record the patient’s name on a sequentially numbered list. This will be the only document to contain any personal information of the patient. It will be stored securely by the Chief Researcher. The number on the list will be the patient’s study number and this number will be recorded on all study documents.

3.3 Assignment of Interventions

3.3.1 Allocation and Randomisation

Patients will be randomly allocated to either the control or the intervention group by computer randomisation. Randomisation and allocation will be managed remotely by the statistician, who will not be involved in patient care, and who will only gain access to study data after completion of data collection.

Block randomisation will be done to ensure that an equal number of patients are assigned to each treatment arm. Random block sizes will be used and the chief investigator, research assistant and treating anaesthetists will be blind to the size of each block.
Sequentially numbered, sealed, opaque envelopes will be prepared by the statistician. This will include a piece of paper indicating the group the patient has been randomised to. The sealed envelope will be handed to the treating anaesthetist on the day of surgery by the Chief Researcher. The Chief Researcher will be responsible for enrolment and assignment of participants.

3.3.2 Blinding

The patient will be blinded to the group they have been randomised to, as the vapour will only be started after induction of anaesthesia. The research assistant administering the post-operative QoR-15 will be blinded to the intervention.

The treating anaesthetist, the Chief Researcher and theatre staff will not be blinded to the intervention, as this would not be practical. All treating anaesthetists and theatre staff will be strongly inculcated not to disclose the allocation status of the participant at any time prior or after the general anaesthetic.

The piece of paper indicating the group will be attached to the Case Report Form. The Case Report Form will be collected by the Chief Researcher and will not be in the patient’s file where it may unblind the patient or research assistant.

There are no circumstances under which unblinding will be permissible.

3.4 Data Collection

3.4.1 Source Documents

The following documents will be used as original source documents from which patient information will be gathered:

- Patient file: history, vital signs, comorbidities, previous anaesthesia and complications.
- Theatre booking list: patient age, type of anaesthesia.
- Blue anaesthetic report card: complete record of the anaesthesia care to the patient.
- Theatre record book: anaesthesia times, basic record of medications given.
- Nursing theatre record: anaesthesia times, recovery times, basic record of medications given.
- Stored history on the Dräger Perseus work station in theatre 11: vapour consumption, anaesthesia times.

3.4.2 Study Documents

The following documents will be used as study documents to record relevant information:

- Case Report Forms (CRF)
  - CRF: Data Collection
  - CRF: Pre-operative QoR-15 form
  - CRF: Post-operative QoR-15 form
• Consent Form
• Patient Information Leaflet
• Standardised Anaesthesia Protocol

The templates for all the above documents are added to this protocol as Appendices.

### 3.4.3 Data Collection Procedures

Patients will be assessed by the chief researcher pre-operatively on the day before surgery. The demographic information on the Data Collection Form (Section A) will be completed. Information will be obtained from the patient’s file, as well as from an interview with the patient. The chief researcher will accurately measure the patient’s weight and height with the available scales and measuring devices in the wards.

Patients will then be asked to complete the QoR-15 in the language of their choice, as a measure of health status over the previous 24 hours.

The following day, the treating anaesthetist will complete the information about the procedure in Section B of the Data Collection Form: anaesthetic time, amount of vapour used, additional medication administered, recovery time, any adverse events (bronchospasm, laryngospasm, post-operative nausea and vomiting and/or other), and whether the prescribed anaesthetic protocol was followed.

Post-operatively, a blinded observer (research assistant) will review the patient on the day following their surgery, prior to discharge. The patients will complete the QoR-15 again.

As follow-up will be done before discharge, retention of patients to follow-up should not present any difficulties.

### 3.5 Data Management

#### 3.5.1 Database Entry

All study documents will be printed. All data will be recorded by hand on paper forms. After recruitment, the Chief Researcher will record the sequential study number on all documents relating to a particular patient.

The data will be captured electronically on the REDCap database by the research assistant (29). REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

Data from each patient will be captured on REDCap sequentially so that the study number correlates with the database entry number.
3.5.2 Data Storage

Study documents will be stored securely by the Chief Researcher. Documents will be kept in a dedicated lever-arch file and will be arranged sequentially according to study number. All study documents relating to a single patient will be stored together.

3.5.3 Data Inspection

In case of incomplete data in Section B of the Data Collection Form, the chief researcher will review the following source documents in the order listed to obtain the information:

| Missing data on medication given intra-operatively: | 1. Blue anaesthesia report card  
2. Nursing theatre record  
3. Theatre record book |
|---------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|
| Missing data on medication given post-operatively: | 1. Blue anaesthesia report card  
2. Nursing theatre record |
| Missing data on anaesthesia start/end times:       | 1. Blue anaesthesia report card  
2. Nursing theatre record  
3. Dräger Perseus stored history  
4. Theatre record book |
| Missing data on vapour start/end times:            | 1. Blue anaesthesia report card  
2. Dräger Perseus stored history |
| Missing data on millilitres vapour used:           | 1. Dräger Perseus stored history |

Patients will complete the QoR-15 forms pre-operatively and post-operatively. The Chief Researcher (pre-operatively) and the research assistant (post-operatively) will review the QoR-15 forms for completeness before leaving the patient’s bedside. If the patient omitted any responses, they will be asked to review and complete the form.

3.6 Data Analysis & Statistical Methods

Demographic and clinical characteristics of patients will be summarised descriptively. Continuous variables (e.g. age or weight) will be summarised by mean, standard deviation, median, interquartile range, minimum and maximum values. Categorical variables (e.g. ethnicity or ASA status), will be summarised by frequency count and percentage calculations.
QoR scores will be considered as a continuous variable and will be summarised as above per treatment group (desflurane and isoflurane).

The null hypothesis for this study is that there is no statistically significant difference in mean post-operative QoR-15 scores of patients receiving isoflurane and desflurane for maintenance of anaesthesia. The alternative hypothesis is that there is a statistically significant difference in mean post-operative QoR-15 scores between patients receiving isoflurane and desflurane.

Based on the available literature, it is assumed that the quality of recovery scores will follow a normal distribution. The data will be inspected for normality prior to analysis.

For the primary objective, the mean and median difference in post-operative QoR-15 scores between the two groups will be tested for significance by the two-sided two-sample t-test and the nonparametric Wilcoxon rank sum test respectively. The mean and median difference between the pre-operative and post-operative QoR-15 scores for the two groups will also be tested for significance by the two-sided two-sample t-test and the nonparametric Wilcoxon rank sum test respectively.

For the secondary objectives, mean and median difference in consumption of vapour and time spent in recovery will be tested for significance by the t-test and Wilcoxon test as above.

Analysis, or comparisons, of subgroups of patients may be performed if it would be of clinical interest; for example, if there appears to be a significant difference in QoR scores between male and female patients.

Results will be presented in tables and graphs or verbatim, as applicable.

All statistical analyses will be performed on SAS (SAS institute Inc, Carey, NC, USA), Release 9.4 or higher, running under Microsoft Windows for a personal computer. Statistical tests will be two-sided and p values ≤0.05 (5%) will be considered significant.

3.7 Monitoring

3.7.1 Data Quality Monitoring

The Chief Researcher will periodically monitor the completed study documents and the database entries. If any problems are found with completion of study documents, training sessions will be arranged in the Department of Anaesthesia.

3.7.2 Interim Analysis

Interim analysis will not be done.
3.7.3 Harms

Adverse events will be recorded on the Data Collection Form. The form makes provision for expected adverse events (bronchospasm, laryngospasm, nausea & vomiting and/or other), as well as for unexpected adverse events. Treating anaesthetists will be instructed to report all adverse events to the Chief Researcher as soon as possible.

Both the control and interventional drugs have been extensively studied and used safely in clinical practice. A brief description of their side-effect profiles, which are very similar, can be found in the literature review. It is therefore not foreseen that many unexpected adverse events will occur. The purpose of the study is not to determine frequency or severity of adverse events, but it is acknowledged that adverse events may occur, and therefore monitoring is important.

Patients with known or suspected susceptibility to Malignant Hyperthermia are excluded from participation in the trial. In the unlikely event that a patient presents with signs and symptoms suggestive of Malignant Hyperthermia, treating anaesthetists will be instructed to stop all volatile agents and to follow departmental emergency management protocols.

3.8 Reliability and Validity

- Validity:
  - Internal validity should be assured on the basis that the anaesthetic techniques will be unchanged between the two groups, except for the anaesthetic vapour. Maintaining the end-tidal vapour concentration at 1MAC for both drugs will prevent disproportionate effects of one drug over the other. The patient population should be homogenous, as only ASA I and II patients presenting for ophthalmological surgery will be included in the study.
  - The chief researcher will counsel each treating anaesthetist prior to them starting a study case to ensure that they follow the required standardised anaesthesia protocol. This will reduce the chance of protocol violations occurring. Any deviations from the standardised protocol will be recorded on the Data Collection Form and will be assessed by the chief researcher.
  - Construct and content validity are assured on the basis that the QoR-15 has been extensively validated in many different languages and for many different surgery types.
  - Data on the Case Report Forms will be inspected for completeness as per section 4.3.5. Incomplete cases will be excluded from analysis.
• Reliability:
  o The QoR-15 is a reliable tool to use. During development of the tool, the internal consistency was measured using Cronbach α and split-half reliability, both of which had satisfactory results.
  o Reproducibility of the QoR-15 was excellent, and exceeded that reported for the QoR-40, indicating that the QoR-15 score can be interpreted with confidence.

3.9 Bias

Randomisation bias will be avoided by using computer randomisation of patients to either the desflurane or isoflurane groups. The randomisation process will be managed by the statistician who is not involved in patient care. Block randomisation will be done to ensure that an equal number of patients are assigned to each treatment arm.

Selection bias will be reduced by using random block sizes and keeping the chief investigator, research assistant and treating anaesthetists blind to the size of each block.

Response or recall bias is possible with the use of a self-reporting questionnaire. To minimise this, the QoR-15 questionnaire will be administered on Day 1 post-operatively, prior to discharge, which will prevent poor memory recall. Blinding of patients will also help to minimise recall bias. Furthermore, the use of a validated scoring tool that uses clear statements and easy-to-understand scoring, like the QoR-15, should also minimise recall bias.

Observer bias will be limited by the observer who will administer the post-operative questionnaire being blinded to the treatment groups.

The QoR-15 has a score range of 0-150, and it was found not to be limited in its capacity to discriminate patients at the extremes of poor and good recovery. A floor or ceiling effect would therefore be unlikely.

4 Ethics and Dissemination

Informed consent will be taken from all participants by the Chief Researcher. Consent forms will be available in English, Afrikaans and Setswana. Only adult patients who can consent to participation will be included in the study.

A patient information leaflet explaining the objectives of the study in layman’s terms has been developed (see Appendix 6.3). This leaflet will be translated into Setswana and Afrikaans once ethical approval has been obtained.

A copy of the patient information leaflet will be given to each patient.

The only document to contain the patient's name will be the sequentially numbered list that will be completed at recruitment. This list will be stored securely by the Chief Researcher. All data will be de-identified: no personal patient information (for example name, date of birth and file number) will be recorded on any study documents (Data Collection Form and QoR-15 forms). Study documents will be numbered sequentially (Data Collection Form
and QoR-15 forms for each patient will have the same number). Paper records will be read into the REDCap System in sequence to ensure the study numbers and the electronic record numbers correspond. All paper documents will be stored securely by the Chief Researcher.

Patients will receive the same standard anaesthesia care, irrespective of which group they are randomised to.

Desflurane is registered at the MCC for the maintenance of anaesthesia. Desflurane is freely available in South Africa and will be used for the registered indication in this study.

Permission to perform the study at Dr. George Mukhari Academic Hospital has been obtained from the hospital superintendent.

Once approval is obtained from the SMU Research Committee, it will be forwarded for approval from the SMU Research Ethics Committee. Once this process is complete, the trial will be registered with the National Health Research Database (NHRD) and on ClinicalTrials.gov.

Any important changes to the protocol after approval (e.g. changes to eligibility criteria, outcomes or analyses) will be communicated to the SMU Research Committee and the SMU Research Ethics Committee.

The results of the trial will be written up by the Chief Researcher for publication in a peer-reviewed academic journal. All supporting documents and de-identified data will be appended as supplements to the main publication.

The results will also be presented at the annual SMU Research Day, and at the annual SASA conference, if selected for presentation.

The Chief Researcher holds current certification in Good Clinical Practice. There are no financial or competing interests for the Chief Researcher. There is no industry involvement in this trial.

5 References


6 Appendices

6.1 SPIRIT Statement Checklist

<table>
<thead>
<tr>
<th>SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*</th>
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<td><strong>Section/item</strong></td>
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<td><strong>Administrative information</strong></td>
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<td>Title</td>
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<td><strong>Introduction</strong></td>
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<td>Outcomes</td>
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<td>Participant timeline</td>
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**Methods: Assignment of interventions (for controlled trials)**

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<th>Allocation:</th>
<th></th>
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<tr>
<td><strong>Sequence generation</strong></td>
<td>16a Method of generating the allocation sequence (e.g., computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (e.g., blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions</td>
</tr>
<tr>
<td><strong>Allocation concealment mechanism</strong></td>
<td>16b Mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned</td>
</tr>
<tr>
<td><strong>Implementation</strong></td>
<td>16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions</td>
</tr>
<tr>
<td><strong>Blinding (masking)</strong></td>
<td>17a Who will be blinded after assignment to interventions (e.g., trial participants, care providers, outcome assessors, data analysts), and how</td>
</tr>
<tr>
<td></td>
<td>17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant’s allocated intervention during the trial</td>
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</table>

**Methods: Data collection, management, and analysis**

<table>
<thead>
<tr>
<th>Data collection methods</th>
<th>18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and a description of study instruments (e.g., questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols</td>
</tr>
<tr>
<td>Data management</td>
<td>19 Plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g., double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol</td>
</tr>
<tr>
<td>Statistical methods</td>
<td>20a Statistical methods for analysing primary and secondary outcomes. Reference to where details of the statistical analysis plan can be found, if not in the protocol</td>
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<td></td>
<td>20b Methods for any additional analyses (e.g., subgroup and adjusted analyses)</td>
</tr>
<tr>
<td></td>
<td>20c Definition of analysis population relating to protocol non-adherence (e.g., as randomised analysis), and any statistical methods to handle missing data (e.g., multiple imputation)</td>
</tr>
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</table>

**Methods: Monitoring**

<table>
<thead>
<tr>
<th>Data monitoring</th>
<th>21a Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed</th>
</tr>
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<tr>
<td></td>
<td>21b Description of any interim analyses and stopping guidelines, including who will have access to those interim results and make the final decision to terminate the trial</td>
</tr>
<tr>
<td>Harms</td>
<td>22 Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct</td>
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<tr>
<td>Auditing</td>
<td>23 Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor</td>
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**Ethics and dissemination**

<p>| Research ethics approval | 24 Plans for seeking research ethics committee/institutional review board (REC/IRB) approval |
| Protocol amendments | 25 Plans for communicating important protocol modifications (e.g., changes to eligibility criteria, outcomes, analyses) to relevant parties (e.g., investigators, RECs/IRBs, trial participants, trial registries, journals, regulators) |</p>
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<tr>
<th>Consent or assent</th>
<th>26a</th>
<th>Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)</th>
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<tr>
<td>Confidentiality</td>
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<td>Declaration of interests</td>
<td>28</td>
<td>Financial and other competing interests for principal investigators for the overall trial and each study site</td>
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<tr>
<td>Access to data</td>
<td>29</td>
<td>Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators</td>
</tr>
<tr>
<td>Ancillary and post-trial care</td>
<td>30</td>
<td>Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation</td>
</tr>
<tr>
<td>Dissemination policy</td>
<td>31a</td>
<td>Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (e.g., via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions</td>
</tr>
<tr>
<td></td>
<td>31b</td>
<td>Authorship eligibility guidelines and any intended use of professional writers</td>
</tr>
<tr>
<td></td>
<td>31c</td>
<td>Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code</td>
</tr>
</tbody>
</table>

**Appendices**

| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates |
|                           |    | With application form |
| Biological specimens      | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyright by the SPIRIT Group under the Creative Commons Attribution-NonCommercial-NoDerivs 3.0 Unported license.*
6.2 Feasibility Questionnaire to Treating Anaesthetists

Feasibility Questionnaire

Date: __/__/__

SECTION A: GENERAL COMMENTS

Dear Colleague,

Thank you for taking the time to complete this questionnaire regarding the standardised treatment protocol for my research study comparing the quality of recovery between patients receiving desflurane and isoflurane for maintenance of general anaesthesia. Please refer to the attached document titled “Standardised Anaesthesia Protocol” and answer the questions below.

Do you think the treatment protocol is practical and easy to follow?

Yes  No

Please share any of your thoughts on the practicality of the protocol:

________________________________________________________________________
________________________________________________________________________
________________________________________________________________________

Would you feel comfortable giving anaesthesia according to this protocol?

Yes  No

If you answered No, please elaborate:

________________________________________________________________________
________________________________________________________________________
________________________________________________________________________

Have you used Desflurane in your clinical practice before?

Yes  No

If you answered No, do you feel the protocol explains well enough how to use it?

Yes  No

If you answered Yes, would you be happy to use it as per the protocol?

Yes  No

If you have any ideas about the prescribed use of Desflurane, please elaborate:

________________________________________________________________________
________________________________________________________________________
________________________________________________________________________

Would you be interested and willing to participate in the study? If yes, please write your name here:

________________________________________________________________________
________________________________________________________________________
________________________________________________________________________

Do you think the protocol covers the management of potential problems well?

Yes  No

Are there any other potential problems you think should be covered in the protocol?

________________________________________________________________________
________________________________________________________________________
________________________________________________________________________

Do you have any other concerns about the protocol?

Yes  No

If you answered Yes, please elaborate:

________________________________________________________________________
________________________________________________________________________
________________________________________________________________________

Overall, do you think the protocol is acceptable?

Yes  No

If you answered No, please elaborate:

________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
Patient Information Leaflet: Participation in Clinical Trial

Study Name: A Randomised Control Trial to Compare Quality of Recovery between Desflurane and Isoflurane Inhalational Anaesthesia in Patients Receiving General Anaesthesia for Ophthalmological Surgery at Dr. George Mukhari Academic Hospital (DIOQR Trial)

Chief Investigator: Dr. Charlé Steyl
Contact Number: 0848009904
Research Assistant: To be confirmed
Format of Study: Randomised, controlled, patient and observer blinded, single-centre superiority trial with two parallel groups.

Dear Sir / Madam,

Thank you for taking part in this research study. This leaflet will give you some background information on how the study will work, and what your role will be.

Background Information:
For you to have a safe operation, your eye surgeon has requested that you have general anaesthesia. This means that you will be sleeping and unconscious during your operation.

The doctor that induces this medical sleep is called an anaesthetist. Most often, anaesthetists will inject medicine into your vein to make you fall asleep, and then once you are sleeping, they will keep you asleep with a medical gas that you breathe in.

There are different medical gases available for use. The one that we use most often at Dr. George Mukhari Academic Hospital is called Isoflurane. There is a new gas available called Desflurane, and it may work better than Isoflurane. It is possible with Desflurane that you may wake up faster and feel more awake after your surgery. In this study, we will try to find out if people feel better when they get Desflurane than when they get Isoflurane.

Why is this research being done?
This research study will look at whether people who receive Desflurane during their anaesthesia feel better the day after surgery than people who receive Isoflurane.

Approval for this study has been given by Dr. George Mukhari Academic Hospital, Sefako Magatho Health Sciences University, and by the Sefako Magatho University Research Ethics Committee (SMUREC).

Why have I been selected?
This study will be done with healthy adults between the ages of 18-80 years, who are coming for eye surgery. You fit this profile. In total, we will ask 170 patients to be part of our study.

When will this research be done?
This study will take place between June-December 2019.

If I take part in this study, how will it affect my treatment?
If you take part in this study, it will not change any of your other treatment. You will receive the same standard anaesthesia care to make you sleep, to treat any pain you may have and to manage complications like nausea and vomiting. Your surgery will take place exactly as planned by your eye surgeon. The only difference will be in the choice of gas used to keep you asleep during the operation. It is important to understand that both of the gases are safe to use.

Will I know which gas I have been given?
No. In order to get good results, the study is designed so that no one will know which gas they received. If you know which gas was used on you, it may change your answers to our questionnaire.

Can I choose the gas that will be used?
No. In order to get good results, you will not be able to choose which gas your anaesthetist uses. Your anaesthetist will receive a sealed envelope on the day of your surgery, and the gas they have to use will be on a piece of paper inside the envelope. That way there is an equal chance for everyone to receive one or the other of the gases.

What do I need to do?
You will be seen on the day before your surgery by the Chief Investigator of this trial, Dr. Charlé Steyl. She will explain all the information in this leaflet to you and answer any questions you may have. You will then complete a questionnaire that will ask you 15 questions. It takes only 3 minutes to complete. On the morning after your operation, before you are discharged from hospital, the Research Assistant, will come to see you and ask you to complete the same 15-point questionnaire again.

Will any of my personal information be used in this trial?
Your participation in this trial is anonymous; this means that none of your personal identifying information (name, date of birth, hospital file number) will be written on any of the study documents. We will collect certain information like your weight, height, age, gender and details of any medical conditions that you may have, but none of this information can be used to identify you.

What will be done with the results from this study?
The results of the study will be published in an academic journal once it is completed.

If I have more questions, who can I contact?
You may contact Dr. Steyl on 0848009904 if you have any further questions.
6.4 Consent Form: English

![Consent Form]

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*Delete whatever is not applicable.*
Standardised Anaesthesia Protocol

6.5 Standardised Anaesthesia Protocol for Treating Anaesthetists

Study Name: A Randomised Control Trial to Compare Quality of Recovery between Desflurane and Isoflurane Inhalational Anaesthesia in Patients Receiving General Anaesthesia for Ophthalmological Surgery at Dr. George Mukhari Academic Hospital (DiQoR Trial)

Chief Investigator: Dr. Charle Steyl
Contact Number: 0849000904
Research Assistant: To be confirmed
Format of Study: Randomised, controlled, patient and observer blinded, single-centre superiority trial with two parallel groups.

Dear Colleague,

Thank you for your willingness to participate in this research study. This document explains how the anaesthesia care will be standardised for patients in this study.

Patient Selection:

Patients will be selected and recruited on the day before surgery by the Chief Investigator. Informed consent for study participation will be taken. Demographic information will be completed on the Case Report Form. Healthy (ASA I & II) adult patients between the ages of 18-80 years, booked for ophthalmological surgery will be considered for inclusion in the trial.

Randomisation:

Patients will be randomly allocated to either the Isoflurane group (control) or the Desflurane group (intervention). On the day of the surgery, you will receive a sealed opaque envelope with the group that the patient falls into. Please follow the instructions below according to the agent to be used. Please attach the randomisation slip to the Case Report Form.

Pre-Medication:

Patients will not receive any pre-medication.

Induction of Anaesthesia:

1. Fentanyl 3 mcg/kg pre-induction
2. Lignocaine 40 mg pre-inductions to minimize Propofol-induced injection pain
3. Propofol 2 mg/kg until induction of anaesthesia
4. Dexmedetomidine 1 mg/kg after induction of anaesthesia to prevent post-operative nausea and vomiting and to reduce opioid consumption
5. Mask ventilation with 8 l/min 100% oxygen until airway is placed
6. Airway management will be with a Laryngeal Mask Airway (LMA), size selected according to patient weight

Isoflurane Group: Maintenance of Anaesthesia:

1. Once the airway is secured, reduce fresh gas flow to 2 l/min.
2. Open the Isoflurane vaporiser and adjust to attain 1MAC.
3. If 1MAC is attained, reduce fresh gas flow to 0.2 l/min 100% oxygen.
4. Adjust the vaporiser to maintain 1MAC throughout the procedure.
5. The use of basal fresh gas flow is intentional to minimise vapor used. When basal flow is used, 100% oxygen is required to match oxygen demand.

Desflurane Group: Maintenance of Anaesthesia:

1. Once the airway is secured, reduce fresh gas flow to 2 l/min.
2. Open the Desflurane vaporiser to 12%.
3. Maintain these settings until 1MAC is reached, about 3 minutes.
4. Now reduce the fresh gas flow to 0.2 l/min 100% oxygen.
5. Adjust the vaporiser to maintain 1MAC throughout the procedure.
6. The use of basal fresh gas flow is intentional to minimise vapor used. When basal flow is used, 100% oxygen is required to match oxygen demand.

Wash-out of Volatile Anaesthetic:

1. At the end of the procedure, close the vaporiser.
2. Increase fresh gas flow to 8 l/min.
3. Remove the Laryngeal Mask Airway when clinically appropriate.

Managing Potential Problems:

1. Should the bag on the anaesthetic machine collapse during basal flow anaesthesia (e.g., because of a poor seal from the LMA, the bag may be re-inflated by pushing the Oxygen Flush button. Vapour flow should be adjusted to maintain 1MAC.
2. Should the ophthalmologist complain that the patient is too light a plane of anaesthesia, the patient may be deepened with a bolus of Propofol 0.5-1 mg/kg.
3. For intra-operative analgesia (for example if patient develop tachycardia or hypertension), administer 50mcg Fentanyl boluses intravenously.
4. For post-operative analgesia in recovery (only if required), administer Tramadol 50-100mg intramuscularly as a bolus.
5. For post-operative nausea (only if required), administer Ondansetron 4mg intravenously as a bolus, followed by Metoclopramide 10mg intravenously after 30 minutes (only if required).

Recording Data on the Case Report Form:

- Please ensure that you complete all the required fields on the Case Report Form.
- Please record any additional medication given to the patient as per above protocol to manage problems like post-operative pain or nausea.
- Please record adverse events on the Case Report Form and inform Dr. Steyl immediately.
- In the unlikely event of Malignant Hyperthermia, please stop all volatiles and follow emergency management protocols.
- Please hand the Case Report Form to Dr. Steyl at the end of the procedure.
6.6 Case Report Form: Data Collection

### Case Report Form: Data Collection

<table>
<thead>
<tr>
<th>Date: <strong>/</strong>/__</th>
<th>Study #: __________</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: __________ years</td>
<td></td>
</tr>
<tr>
<td>Gender:</td>
<td>Male</td>
</tr>
<tr>
<td>Weight:</td>
<td>kg</td>
</tr>
<tr>
<td>ASA Status:</td>
<td>I</td>
</tr>
<tr>
<td>Risk for PONV:</td>
<td>Female</td>
</tr>
<tr>
<td>Smoking History:</td>
<td>Non-smoker</td>
</tr>
<tr>
<td>Comorbidities:</td>
<td>None</td>
</tr>
<tr>
<td>Cerebrovascular Disease</td>
<td>Renal Disease</td>
</tr>
<tr>
<td>Details of Condition:</td>
<td>Any Anaesthesia in the Past Month?</td>
</tr>
<tr>
<td>If YES: General</td>
<td>Regional</td>
</tr>
<tr>
<td>Any Complications?</td>
<td>Yes</td>
</tr>
<tr>
<td>If YES, Describe:</td>
<td></td>
</tr>
</tbody>
</table>

#### SECTION B: INFORMATION ABOUT PROCEDURE:

<table>
<thead>
<tr>
<th>Group:</th>
<th>Desflurane</th>
<th>Isoflurane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous Induction Time:</td>
<td></td>
<td>End of Anaesthesia:</td>
</tr>
<tr>
<td>Time Vapour Started:</td>
<td></td>
<td>Time Vapour Stopped:</td>
</tr>
<tr>
<td>Millilitres of Vapour Used:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propofol at Induction:</td>
<td></td>
<td>mg</td>
</tr>
<tr>
<td>Fentanyl at Induction:</td>
<td></td>
<td>mcg</td>
</tr>
<tr>
<td>Intra-op Propofol Top-up:</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Number of top-ups given:</td>
<td></td>
<td>Total Dose:</td>
</tr>
<tr>
<td>Intra-op Fentanyl Top-up:</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Number of top-ups given:</td>
<td></td>
<td>Total Dose:</td>
</tr>
<tr>
<td>Post-Op Ondansetron:</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Time:</td>
<td></td>
<td>Dose:</td>
</tr>
<tr>
<td>Post-Op Metoclopramide:</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Time:</td>
<td></td>
<td>Dose:</td>
</tr>
<tr>
<td>Post-Op Tramadol:</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Adverse events:</td>
<td>Bronchospasm</td>
<td>Laryngospasm</td>
</tr>
<tr>
<td>Other (specify below):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time into Recovery:</td>
<td></td>
<td>Time out of Recovery:</td>
</tr>
<tr>
<td>Total time in Recovery:</td>
<td>min</td>
<td></td>
</tr>
<tr>
<td>Anaesthesia administered as per study protocol:</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>If no, please describe modification:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
6.7 Case Report Form: QoR-15

**QoR-15 Patient Survey**

Date: ___ / ___ / ___  
Study #: ____________

Pre-Operative [ ]  
Post-Operative Day 0 [ ]  
Post-Operative Day 1 [ ]

**PART A**

**How have you been feeling in the last 24 hours?**

(0 to 10, where 0 = none of the time [poor] and 10 = all of the time [excellent])

<table>
<thead>
<tr>
<th></th>
<th>None of the time</th>
<th>All of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Able to breathe easily</td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
</tr>
<tr>
<td>2. Been able to enjoy food</td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
</tr>
<tr>
<td>3. Feeling rested</td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
</tr>
<tr>
<td>4. Have had a good sleep</td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
</tr>
<tr>
<td>5. Able to look after personal toilet and hygiene unaided</td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
</tr>
<tr>
<td>6. Able to communicate with family or friends</td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
</tr>
<tr>
<td>7. Getting support from hospital doctors and nurses</td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
</tr>
<tr>
<td>8. Able to return to work or usual home activities</td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
</tr>
<tr>
<td>9. Feeling comfortable and in control</td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
</tr>
<tr>
<td>10. Having a feeling of general well-being</td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
</tr>
</tbody>
</table>

**PART B**

**Have you had any of the following in the last 24 hours?**

(10 to 0, where 10 = none of the time [excellent] and 0 = all of the time [poor])

<table>
<thead>
<tr>
<th></th>
<th>None of the time</th>
<th>All of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Moderate pain</td>
<td>10 9 8 7 6 5 4 3 2 1 0</td>
<td>10 9 8 7 6 5 4 3 2 1 0</td>
</tr>
<tr>
<td>2. Severe pain</td>
<td>10 9 8 7 6 5 4 3 2 1 0</td>
<td>10 9 8 7 6 5 4 3 2 1 0</td>
</tr>
<tr>
<td>3. Nausea or vomiting</td>
<td>10 9 8 7 6 5 4 3 2 1 0</td>
<td>10 9 8 7 6 5 4 3 2 1 0</td>
</tr>
<tr>
<td>4. Feeling worried or anxious</td>
<td>10 9 8 7 6 5 4 3 2 1 0</td>
<td>10 9 8 7 6 5 4 3 2 1 0</td>
</tr>
<tr>
<td>5. Feeling sad or depressed</td>
<td>10 9 8 7 6 5 4 3 2 1 0</td>
<td>10 9 8 7 6 5 4 3 2 1 0</td>
</tr>
</tbody>
</table>