PROTOCOL TITLE

MONITOR - MethOxyfluraNe in InTerventiOnal Radiology

SPONSOR
Department of Interventional Radiology, Liverpool Hospital

CONFIDENTIAL

STATEMENT OF COMPLIANCE

This document is a protocol for a clinical research study. The study will be conducted in compliance with all stipulations of this protocol, the conditions of ethics committee approval, the NHMRC National Statement on Ethical Conduct in Human Research (2007) and the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95).

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1. SUMMARY

1.1 Synopsis

Study Title	MONITOR- MethOxyfluraNe in Interventional Radiology
Aims/Objectives	Aim: To improve the quality of care in interventional radiology by minimising pain and anxiety in everyday procedures whilst optimising resources for Liverpool Hospital and SWS LHD. Primary: to assess the efficacy and safety of methoxyflurane in IR, if methoxyflurane leads to decreased levels of pain and anxiety in common IR procedures, if methoxyflurane is more effective in certain procedures, if the efficacy of methoxyflurane is related to procedure length, if methoxyflurane has an effect on procedure time or time to discharge. Secondary: to assess the importance of patient-controlled analgesia for patients, clinician/proceduralist satisfaction with methoxyflurane in IR procedures.
Study design	Prospective double blind randomised controlled study comparing methoxyflurane (Penthrox®) vs placebo.
Planned sample size	250-500 patients.
Inclusion criteria	Patients undergoing deep tissue core biopsy and insertion or removal of portacaths in the interventional radiology department at Liverpool Hospital who are hemodynamically stable, afebrile and able to consent.
Exclusion criteria	Patients with renal impairment (eGFR<50), liver dysfunction, pregnancy, requiring definite IV sedation, who opt out or refuse or where it would be clinically inappropriate to blind to the possibility of no sedation.
Study procedures	Patients will be given an unlabeled green whistle loaded with methoxyflurane or placebo (empty). This will be blinded to the proceduralist, patient, nurses and radiographers. The designated study nurse and SRMO will take care of the blinding process, loading the whistles according to the randomisation process. Patients will be assessed through standardised questionnaires pre and post procedure in addition to monitoring levels of analgesia and anxiolysis at discrete time points during the procedure (5 minute intervals). A proceduralist questionnaire will also be conducted.

	Procedure time, adverse events or complications will also be recorded for correlation and analysis.
Analysis considerations	Continuous variables will be summarised using mean (SD) or median (IQR) and comparison between study groups will be made with student T test or Mann-Whitney U test. Categorical variables will be recorded as counts and percentages and comparisons between study groups will be made using chi-square or Fisher's exact test. Calculated P-values will be two tailed with $P<0.05$ indicating statistical significance. Non-inferiority analysis will also be implemented.
Study duration	Data collection 6 months. Expected study duration 12 to 18 months.

1.2 Study investigators

Coordinating Principal Investigator:
Name: Dr Ross Copping
Position; Interventional radiology post graduate fellow
Institution: Interventional Radiology, Liverpool Hospital

Principal Investigator:
Name: Dr Paul Balamon
Position; Interventional Radiology SRMO
Institution: Interventional Radiology, Liverpool Hospital

Supervising Investigator:
Name: Dr Jules Catt
Position; Interventional Radiology Consultant
Institution: Interventional Radiology, Liverpool Hospital

Associate investigator:
Name: Dr Louise Wei
Position: Interventional Radiology SRMO
Institution: Interventional Radiology, Liverpool Hospital

1.3 Funding

No funding has been requested nor is required for this project. All investigators are contributing their support willingly and voluntarily in their own time.

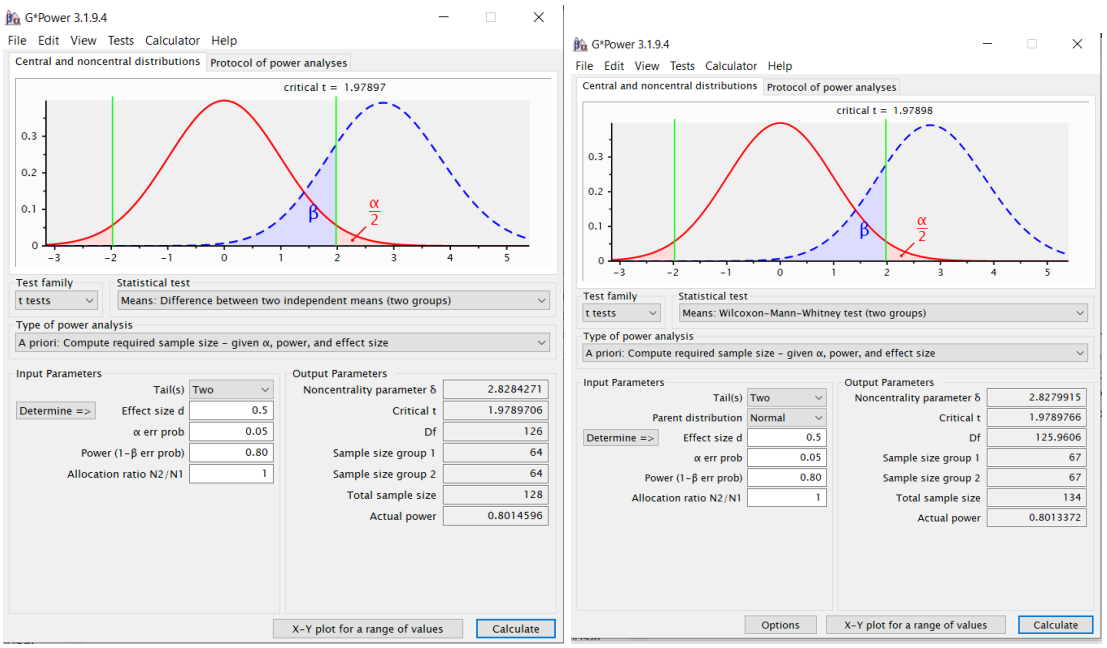
Inhaled Methoxyflurane in the form of Penthrox® is already used on a daily basis in the interventional radiology department and is dispensed and used in compliance with departmental and hospital standards of care. This medication is imprest stock and all the clinical staff in Liverpool interventional radiology have had in-service training on how to use the “green whistle” in a safe manner.

Medical Developments International (MDI) have already developed and provided us with training whistles, which look exactly the same as the Penthrox® device except that they are empty rather than being loaded with the methoxyflurane. These empty whistles are already stocked and used to train staff about how to use the Penthrox® device and could be used as the placebo for the trial. MDI has agreed to provide these for the duration of the study at no cost.

1.4 Statistical analysis

Senior biostatistician Wei Xuan (MSc MAppStat PhD) was consulted for the trial.

Responses will be recorded according to a likert scale (0 to 10) for pain and anxiety prior to the procedure, intra procedurally and post procedure and compared between the two study groups. Mean, median and standard deviations will be calculated from these responses.The 2 sample T-test with 95% confidence interval will be employed from the data collected. The expected variation between the two study groups would be greater than 1.5 to in order to infer a significant difference.



A statistical power analysis was performed for sample size estimation, with a small effect size of 0.2, using Cohen’s (1988) criteria. With an alpha = .05 and power = 0.80, the projected sample size needed with this effect size (GPower 3.1) is approximately N = 134 for the Wilcoxon-Mann-Whitney test of difference between

two independent groups. Thus, our proposed sample size of N+X will be more than adequate for the main objective of this study and should also allow for expected attrition (X being the number of people added due to attrition) [13,14].

2. BACKGROUND AND RATIONALE

Patient-controlled analgesia (PCA) has greatly improved the patient experience postoperatively and greatly enhanced recovery [1]. PCA can provide effective analgesia in a timely fashion [1]. Methoxyflurane has largely been used as an opioid sparing, safe and feasible alternative to traditional procedural sedation in a variety of clinical settings. Methoxyflurane has been used in the acute management of pain including trauma and prehospital setting [2-3]. It was also shown utility in the procedural setting with a role in colonoscopies, burn wound care and dental clinics [4-6].

The pharmacokinetics of methoxyflurane allows for a rapid onset and offset time with minimal toxicity, facilitating its role in a variety of healthcare settings [3,5,6]. Other benefits include opioid sparing analgesia in lieu of increased opioid dependency and other agents conventionally used for procedural sedation which carry risks of respiratory depression and necessitate an extended recovery period of post-procedure [4, 7, 8].

Timely access to analgesia has become the focus of pain management in the hospital setting particularly in the form of PCA. Adequate analgesia is also essential for procedural success [4]. Most interventional radiology procedures have a modest analgesia and sedation requirement and procedures typically have a short duration therefore pharmacological therapies present as a suitable adjunct. PCA in the form of methoxyflurane offers a safe and viable solution to providing short-term pain relief. It is an opioid-sparing alternative that is easier to administer than nitrous oxide, being delivered via a self-contained single use portable inhaler. Traditionally, proceduralists and sedation nurses have managed administration of analgesia but there is evidence to suggest that allowing patients to be actively involved in their own pain relief may be therapeutic in itself and empowering them may also lead to reduced levels of pain and improved patient satisfaction [11]. Furthermore, it has shown to be effective for central line placement in interventional radiology [12].

Methoxyflurane has been used in Australia for the last 40 years and was in regular use in 140 individual hospitals across Australia in 2020. In Australia, methoxyflurane is TGA registered for:

1. Emergency relief of pain by self-administration in conscious hemodynamically stable patients with trauma and associated pain, under supervision of personnel trained in its use
2. The relief of pain in monitored conscious patients who require analgesia for surgical procedures.

Methoxyflurane has been used regularly in the interventional radiology department at Liverpool Hospital over the last 2 years. There has been overwhelmingly positive feedback from patients in a preliminary intradepartmental audit collected for quality assurance and there have been no adverse events during this time. Methoxyflurane has consistently demonstrated non-inferiority in periprocedural levels of pain reported by patients and procedural success. In addition, it has freed up nursing staff that would usually be required for monitoring of IV sedation to be more attentive to other

aspects of patient care and comfort. Because of the optimisation of resources, it has also reduced waiting times for procedures. Despite these benefits, its use has not yet been formally validated in the context of interventional radiology, although studies have shown its benefit as an analgesic agent in a variety of other clinical contexts and procedures with similar analgesia requirements [2-6]. For these reasons, we aim to investigate the safety and efficacy of methoxyflurane for interventional radiology procedures and formally validate our clinical experience.

3. STUDY AIMS/OBJECTIVES

Aim: To improve the quality of care in interventional radiology by minimising pain and anxiety in everyday procedures whilst optimising resources for Liverpool Hospital and SWS LHD.

Primary objectives:

- to determine the efficacy and safety of methoxyflurane use in interventional radiology procedures
- to determine if the use of methoxyflurane results in decreased levels of pain and anxiety in common interventional procedures compared to local anaesthesia alone
- to determine if methoxyflurane is more effective for certain procedures over others compared to local anaesthesia alone
- to determine if the efficacy of methoxyflurane is related to the length of procedure

Secondary objectives:

- to assess the importance of patient-controlled analgesia and how important it is for patients to feel in control of their pain and anxiety in interventional procedures
- to assess clinician/proceduralist satisfaction with the use of methoxyflurane in interventional radiology procedures

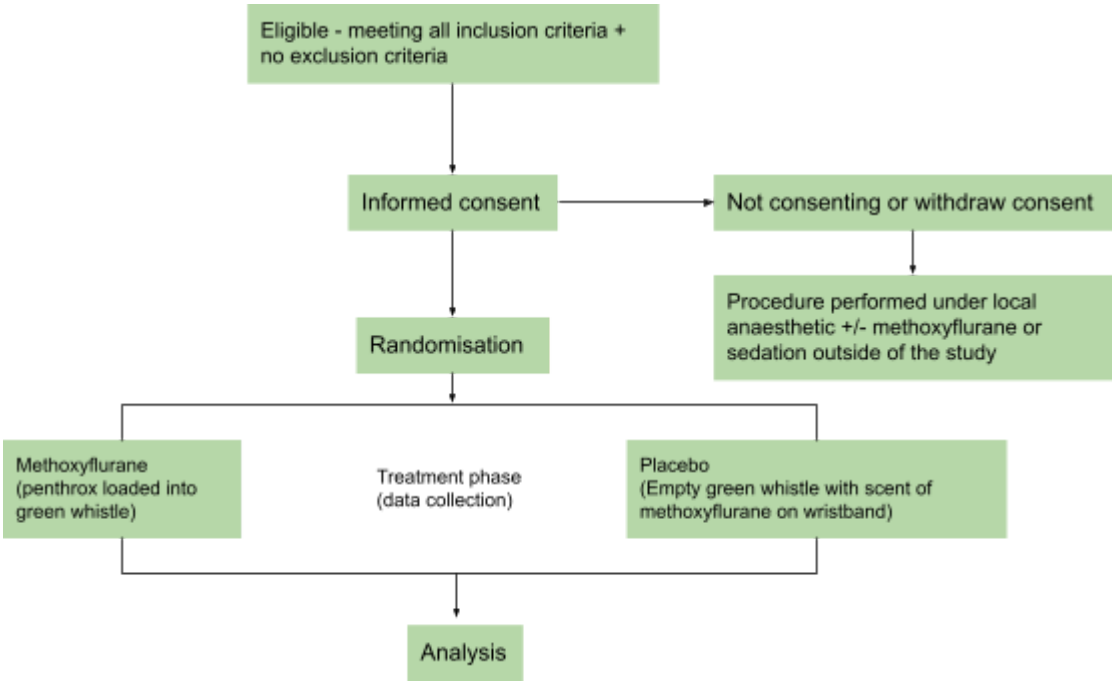
Hypotheses: We hypothesise, based on anecdotal experience, preliminary data and evidence in the literature, that methoxyflurane (Penthrox®) is safe and effective for general interventional radiology procedures. In addition, we propose that patient-centred analgesia leads to improved patient comfort and satisfaction.

The primary outcomes to be measured are levels of pain and anxiety and patient satisfaction between the two groups.

4. PARTICIPATING SITES

Liverpool Hospital.

5. STUDY DESIGN



The MONITOR trial is a prospective double-blind randomised control study comparing the efficacy of methoxyflurane (Penthrox®) vs placebo for interventional radiology procedures. All patients booked for these elective procedures will be screened for the inclusion and exclusion criteria. The patient's blood test results on EMR/powerchart will be reviewed, which is already a requirement for these procedures and in accordance with standard of care.

All patients undergoing deep tissue core biopsy and insertion or removal of portacaths in the Liverpool Hospital Interventional Radiology Department who meet all inclusion criteria and none of the exclusion criteria will be offered enrolment in the study and consented accordingly.

Once the patient has been consented and enrolled in the study, they will be randomised by the senior resident medical officer into one of the 2 study arms according to the randomisation algorithm (predetermined according to randomizer.org). This will then be kept confidential, disclosed only to the delegated clinical trials nurse who will give the patient a Penthrox® "green whistle" loaded with methoxyflurane (treatment) or an empty training "green whistle" (placebo). The Penthrox® green whistle loaded with methoxyflurane is indistinguishable from the training green whistles provided by the company (MDI) which will be used as the placebo for our study. There is no difference in the stickers and labelling. The most characteristic feature of the medication to the patient is the smell, so a few drops of methoxyflurane will be added to the wristband of the empty placebo "green whistle" in order to mimic this and create a more robust placebo. This is well below the amount required for any therapeutic effect and a technique used in other blinded published studies of methoxyflurane. The loaded green whistle (with either methoxyflurane or placebo) will then be given to the patient in the procedure room. Everyone in the procedure room, including proceduralists, radiographers and nurses, as well as the patient will remain blinded to the contents of the whistle. The senior resident medical

officer will then collect the data sheet post completion and record the contents of the whistle (either methoxyflurane or placebo) on the data collection sheet. This is also recorded next to the patient's allocated study number to ensure the right study arm is documented. Only the nursing staff (including the delegated study trial nurse) have access to methoxyflurane, which is stored in accordance with S4 medication protocol. The Penthrox® inhaler is a registered medical device (ARTG number 136219) that complies with GMP and can be lawfully supplied in Australia.

5.1 Study Type

Prospective double-blind randomised control study.

5.2 Expected Study Duration

Data collection for the study will be carried out over 6 months. During this time, it is expected that between 250 and 500 patients will be enrolled in the study.

5.3 Data Source and Population

Pilot data has qualitatively appraised the experience of approximately 50 participants in an internal audit. The expected duration of the study is 6 months with expected recruitment to include 250-500 participants subject to the inclusion criteria. This study will recruit from a single site and department; namely the Liverpool Hospital Interventional Radiology Department.

Consent enrolment and participation in patient experience questionnaires (PEQ) for this study will be offered in a culturally appropriate format. PEQs will be offered to cater for a culturally and linguistically diverse participant cohort. The use of standardised graphics accepted in the literature for pain scores and patient satisfaction surveys will be utilised for a culturally and linguistically diverse participant cohort. The PEQ form will include a visual-analogue scale for collection of research data, negating the need for the interpreters service in data collection.

The patients will be assessed through standardised questionnaires pre and post procedure in addition to monitoring levels of analgesia and anxiolysis at discrete time points during the procedure (5 minute intervals). Pain and anxiety will be assessed using visual analogue scales, ranging from 0 (no pain or anxiety at all) to 10 (worst pain or anxiety imaginable). The pre procedure questionnaire will be performed at the time of procedural consent and the post procedure will be performed one hour post procedure just prior to discharge home. A proceduralist questionnaire will also be conducted. The questionnaires/data collection sheets have been attached as *appendix 2*. The procedure time, any adverse events or complications will also be recorded for correlation and analysis. If the patient withdraws consent or requires 'rescue analgesia' , they will be excluded from the main component of the analysis as this would confound direct comparison between methoxyflurane and the control, however this will be included in overall discussion and analysis in order to identify any issues or areas for improvement. This has been rare in clinical practice but would form an important part of the analysis when considering its use longer term. This will be clearly communicated at the time of consent and outlined in the participants information sheet.

5.4 Recruitment and Screening

All patients undergoing deep tissue biopsy and insertion or removal of portacaths in the Liverpool Hospital Interventional Radiology Department will be offered participation in the study. Participation in the study will not affect any other aspects of their treatment or care. Patients can opt out of the trial at any time.

Patients will be given a standardised questionnaire before and after the procedure to assess their experience. Their levels of analgesia and sedation will also be assessed at discrete time points during the procedure by the sedation nurse.

5.5 Inclusion Criteria

All patients undergoing deep tissue biopsy and insertion or removal of portacaths in the Liverpool Hospital Interventional Radiology Department will be offered participation in the study. Methoxyflurane is routinely used as an adjunct to local anaesthesia for these procedures in our department. Patients must be over 18 years of age and have capacity to provide consent. Written informed voluntary consent will be obtained. Patients must be hemodynamically stable and afebrile.

- deep tissue biopsies
- portacath insertions
- portacath removal
- able to consent
- hemodynamically stable
- afebrile

5.6 Exclusion Criteria

Low acuity outpatient procedures have deliberately been selected for the purposes of this study. These typically require low levels of sedation. Patients who require definite IV sedation, who are pregnant or in whom it is not appropriate to blind to no sedation will be excluded from the study.

The research project will be discussed with the patients at the time of consent. It will be clearly explained that they may opt out of the study or deny/withdraw consent at any stage. Patients unable to provide informed, voluntary, competent consent will be excluded. Any patient with allergy or prior adverse reaction to methoxyflurane will not be given methoxyflurane and therefore excluded from the study.

Patients with impaired renal function (eGFR<50) or liver dysfunction will be excluded as per standard of care for the safe administration of Penthrox® based on the Australia Medical Handbook, Liverpool Hospital protocol and the Australian Therapeutic Goods Administration.

- renal impairment (eGFR<50)
- liver dysfunction
- pregnancy
- opt out or refusal
- definite IV sedation required
- clinically inappropriate to blind to possibility of no additional analgesic adjunct

5.7 Consent Process

Capacity to provide research and procedural consent will be clinically assessed on admission to the interventional radiology department. Methoxyflurane ("the green whistle") will be discussed with the patient by the interventional radiology fellow or senior resident medical officer where requested, as per standard practice, and information will be provided to the patient where requested.

At the time of enrollment the Participant Information Sheet and Consent Forms will be provided to the patient; the 'About the Trial' has been modelled after the SWSLHD website proformas (https://www.swslhd.health.nsw.gov.au/ethics/forms.html) to convey the information about the trial, adequate time will be given to patient and any questions will be answered by the trial personnel present. The patient will be informed about the role of the research to the level of their understanding, the use of methoxyflurane in clinical practice (including risks, benefits and alternatives), and what they can expect if they agree to participate (including any potential risks, rights and responsibilities).

The patient will be provided enough time to make an informed choice and all questions asked will be answered facilitating the consent discussion. They will be reassured that they are able to withdraw/revoke consent at any point without penalty. If the patient is agreeable to participate in the study at this point, informed written consent will be obtained and documented in the patients' medical records and line with ICH-GCP guidelines.

It will be ensured that consent is informed, voluntary and competent in accordance with *National Statement Chapters 2.2.9, 4.3.* If the patient requires the use of an interpreter, an impartial witness will be present to ensure the informed consent discussion has taken place. The impartial witness will then be instructed to sign the informed consent document. The Investigate conducting the consent discussion will document this discussion in the patients' medical records inclusive of the use of an interpreter to facilitate the discussion.

5.8 Study Procedures

Methoxyflurane (Penthrox®) is already used as the standard of care for many interventional radiology procedures at Liverpool Hospital, and has been used regularly in interventional radiology over the last 2 years. An internal departmental audit for quality assurance has shown very positive feedback from patients in terms of anxiolysis and analgesia and we aim to formally validate its use for interventional radiology procedures through this research.

Methoxyflurane has been in routine use throughout the interventional radiology department for over 2 years. All the medications in this study are part of an impressed stock located in the interventional radiology department, stored in accordance with S4 drug requirement. The supply and restocking procedures are established as per SWSLHD medication supply guidelines. This study does not require access to the pharmacy. This study aims to collect data on the efficacy of inhaled methoxyflurane. This study will not affect the established pharmacy department procedures currently in place for prescribing, dispensing, storing, restocking or discarding of these medications. These medications are already in routine use at Liverpool hospital.

All patients undergoing deep tissue biopsy and insertion or removal of portacaths in the Liverpool Hospital Interventional Radiology Department will be offered participation in the study. As well as being part of routine practice and some of the most commonly performed procedures in IR, these are the most standardised and reproducible, therefore aiming to minimise any variables outside of procedural sedation or analgesia. They are all low acuity outpatient procedures that typically require low dose sedation in conjunction with local anaesthesia.

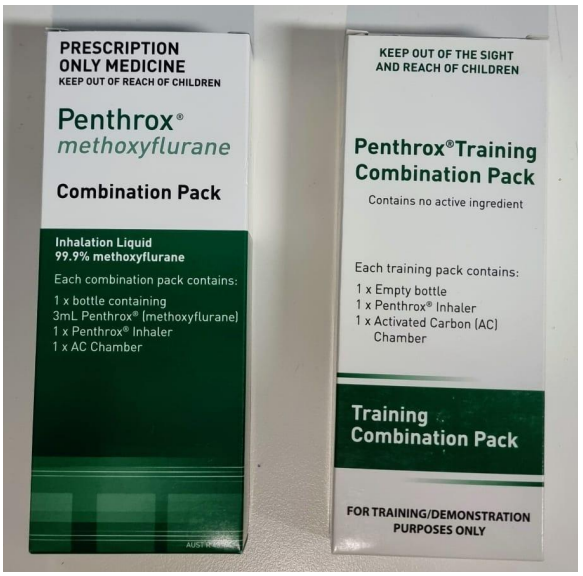
Potential patients will be enrolled into the study just after informed consent has been completed and the patient has met all inclusion criteria and none of the exclusion criteria. The patient will be assigned a randomised study code for de-identification and anonymisation which will be subsequently recorded on all study documents.

Once the patient has been consented and enrolled in the study, they will be randomised by the senior resident medical officer into one of the 2 study arms according to the randomisation algorithm (predetermined according to randomizer.org). This will then be kept confidential, disclosed only to the delegated clinical trials nurse who will give the patient a Penthrox® “green whistle” loaded with methoxyflurane (treatment) or an empty training “green whistle” (placebo). The Penthrox® green whistle loaded with methoxyflurane is indistinguishable from the training green whistles provided by the company (MDI) which will be used as the placebo for our study. There is no difference in the stickers and labelling. The most characteristic feature of the medication to the patient is the smell, so a few drops of methoxyflurane will be added to the wristband of the placebo in order to mimic this and create a more robust placebo. This is well below the amount required for any therapeutic effect and a technique used in other blinded published studies of methoxyflurane. The loaded green whistle (with either methoxyflurane or placebo) will then be given to the patient in the procedure room. Everyone in the procedure room, including proceduralists, radiographers and nurses, as well as the patient will remain blinded to the contents of the whistle. The senior resident medical officer will then collect the data sheet post completion and record the contents of the whistle (either methoxyflurane or placebo) on the data collection sheet. This is also recorded next to the patient’s allocated study number to ensure the right study arm is documented. Only the nursing staff (including the delegated study trial nurse) have access to methoxyflurane, which is stored in accordance with S4 medication protocol. The Penthrox® inhaler is a registered medical device (ARTG number 136219) that complies with GMP and can be lawfully supplied in Australia. The Penthrox® inhaler has been in routine use in Liverpool hospital for over 2 years in accordance with hospital and NSW health policies. Patients will receive education on how to use the inhaler device by trained nursing staff; as per standard of care. Please note that in-service education sessions have been held for all nursing, radiography and medical staff in Liverpool interventional radiology department in accordance with existing Liverpool hospital and NSW Health standard of care for the safe use of Penthrox®.

The patients will be assessed through standardised questionnaires pre and post procedure in addition to monitoring levels of analgesia and anxiolysis at discrete time points during the procedure (10 minute intervals). Pain and anxiety will be assessed using visual analogue scales ranging from 0 (no pain or anxiety at all) to 10 (worst pain or anxiety imaginable). The pre procedure questionnaire will be performed at the

time of procedural consent and the post procedure will be performed one hour post procedure just prior to discharge home. A proceduralist questionnaire will also be conducted. The questionnaires/data collection sheets have been attached as *appendix 2*. The procedure time, any adverse events or complications will also be recorded for correlation and analysis. If the patient withdraws consent, their data will be removed and excluded from the study, and this will be clearly communicated at the time of consent and outlined in the participants information sheet. If a patient requires 'rescue analgesia', they will be excluded from the main analysis group and discussed in the overall analysis.

Statistical analysis will be performed by the investigators using Microsoft Excel and SPSS. Continuous variables will be summarised using mean (standard deviation) or median (interquartile range) where appropriate and comparison between the study groups will be made using the student T test or the Mann-Whitney U test. Categorical variables will be recorded as counts and percentages and comparisons between the study groups will be made using chi-square or Fisher's exact test. Calculated P-values will be two tailed with $P<0.05$ indicating statistical significance. Non-inferiority analysis will also be implemented with significance level (alpha) 5%, power 90%, percentage success expected in each group >90% and non inferiority limit (d) 20%.



Treatment whistle (left) and training whistle (right).

5.9 Randomisation

Randomisation will be predetermined and generated by a randomisation engine (randomizer.org) in order to allocate participants into two groups, either Penthrox® (inhaled methoxyflurane via “the green whistle”) or placebo (empty training “green whistle”). The results will be stored securely in sealed envelopes in the interventional radiology department, consecutively numbered and only accessible to the clinical nurse educator/study nurse. Once a patient is assessed and enrolled at the time of consent, the envelope will be opened revealing the allocated study group only to the study nurse. The proceduralist, assistants, scrub and scout nurses, sedation nurse and patient will be blinded to the process and the study group.

6. TISSUE COLLECTION/BIOBANKING

Not applicable.

7. ETHICAL CONSIDERATIONS

7.1 Study Procedure Benefits

Landmark studies have found methoxyflurane (Penthrox®) to be a safe and well-tolerated addition to current procedural sedation agents, in conjunction with local anaesthesia [2-7]. There is also emerging evidence to support the use of patient-controlled analgesia/sedation for procedures, including in interventional radiology, rather than the standard proceduralist-controlled analgesia. It has been proposed that this can avoid issues related to under or overdosing and empowering patients with control over their own levels of pain or anxiety may be therapeutic in itself. Safe analgesic agents such as methoxyflurane ("the green whistle") are widely used in the community (e.g. surf life saving, first aid, emergency), highlighting their safety without the need for monitoring [2-7].

Furthermore, many patients know or have heard of the "green whistle", providing an additional layer of comfort or reassurance to patients. In addition, methoxyflurane does not require additional staffing for monitoring of sedation that is required for intravenous sedation (such as midazolam or fentanyl), thereby reducing the barriers to patient comfort whilst easing the burden/drain on resources required for these high volume procedures. This should translate to optimisation of resources in the interventional radiology department, Liverpool Hospital and SWS LHD while improving overall patient comfort and care.

The role of Penthrox® in procedural analgesia has a significant body of research supporting it; as a safe PCA device [2-7]. The progress of analgesia models centres on patient control, timely administration and opioid sparing alternatives [1,7,8]. Methoxyflurane meets all of these criteria; it is a safe effective non-opioid analgesia that provides strong analgesia within minutes and can be safely used by the patient if and when they need it. This instant administration of analgesia and the ability of the patient to titrate their analgesia by increasing frequency or dose provides layers of control to the patient. This control could lead to a better patient experience and support evidence that suggests there are increased levels of patient satisfaction associated with patient-directed analgesia. Methoxyflurane is generally used in the pre-hospital, dental and clinical setting and applying this analgesic to the highly controlled and monitored environment of an interventional radiology suite should allow better levels of pain control than local anesthesia alone. Its role as a non-sedating agent in comorbid patients may also prove a safer practice. This inhaled agent has a rapid onset and offset allowing a faster recovery for patients thus translating to avoiding prolonged periods of observation required with IV analgesics and reduced unnecessary occupancy of hospital beds even in the outpatient/recovery setting.

So far, our experience with methoxyflurane has been supportive of these benefits, which has been reflected in proceduralist, nursing and patient feedback. Of the patients that participated and responded to a recent intradepartmental audit for quality assurance, 73% reported a positive experience with methoxyflurane and 79% would recommend it for others, and there have been no significant adverse events or complications since commencing its use in interventional radiology.

7.2 Study Procedure Risks

The current standard of care in terms of analgesia in the Liverpool Hospital Interventional Radiology Department for patients undergoing deep tissue biopsy and insertion or removal of portacaths is local anaesthesia and methoxyflurane. Methoxyflurane was introduced 2 years ago as another option for analgesia, as an alternative to IV sedation or local anesthesia alone, with successful results. Due to the sedative effect and higher risk of respiratory depression and hypotension in intravenous procedural sedation, methoxyflurane carries several advantages. The pilot data on the role of methoxyflurane has found it to be an opioid sparing adjunct to local anaesthesia with rapid onset and offset times and faster recovery times. These findings are consistent with a large body of evidence that illustrates the role of methoxyflurane in intraprocedural analgesia [1-6]. Risks in this study include over-analgesia or under-analgesia or adverse reactions to methoxyflurane.

Over-analgesia

The risk of over-analgesia is mitigated by several factors. Primarily, the methoxyflurane in the Penthrox® device has a 3 mL dose, which is not sedative nor nephrotoxic at these levels via the inhalation device. The patient will be regularly monitored by the proceduralist and sedation nursing, in addition to assessment of pain, anxiety and sedation at 5-minute intervals, (please see “master data collection form v3 (Penthrox® VS PLACEBO)”). If over-analgesia, sedation or other adverse side effects are encountered, the study will be aborted to ensure the safety of the patient. Previously, patients have been escalated to intravenous procedural sedation, including opioids and benzodiazepines, which carry much higher risks of over analgesia, and adverse events including over-sedation and even respiratory depression [8].

Under-analgesia

There is also a possibility of under-analgesia in participants receiving methoxyflurane or a placebo. Local anaesthetic administered alone has been the standard of care (and is in many other centres). Thus the placebo group will receive standard of care in addition to regular monitoring of pain and analgesia levels; hence there should be no difference between the placebo group and current standard of care with the aim of the study being to quantify if the methoxyflurane arm experienced a benefit from the patient controlled analgesia. The participants randomised to the placebo arm will receive the current standard of care analgesia (local anaesthesia alone) in addition to the placebo green whistle. The participants randomised to the methoxyflurane arm will receive a green whistle containing methoxyflurane in addition to the current standard of care analgesia (local anaesthesia).

Upon enrollment, participants will receive education on safe use of the green whistle. They will also be instructed on how to occlude the dilution hole with their finger and deliver an increased dose of methoxyflurane or placebo to achieve optimal analgesia. Education on use of the green whistle will be given upon enrolment to the study, and sedation nurses will require participants to demonstrate the use of the device prior to the commencement of the procedure to verify correct technique. Participants may also be instructed on use of the green whistle throughout the duration of the procedure as required. Patients' pain and anxiety levels will be monitored regularly throughout the duration of the procedure (5 minute intervals, please see “master data collection form v3 (Penthrox® VS PLACEBO)”). Enrollment in the methoxyflurane or

placebo arm of this study will necessitate more frequent pain and anxiety monitoring compared to the current standard of care. This more robust procedural monitoring alone will alert the procedualist and sedation nurse of potential under-analgesia and facilitate more timely access to analgesia, be it via the green whistle in the trial or rescue analgesia outside the trial. This high frequency of pain and anxiety monitoring alone will serve as an effective safety mechanism in the trial procedures to minimise under-analgesia in addition to facilitating rapid access to rescue analgesia as clinically indicated.

If a patient reports under-analgesia or uncontrolled levels of pain not relieved by the Penthrox® inhaler rescue analgesia will be administered as per the pre-existing standard of care. The procedure may be aborted if deemed clinically appropriate; the patient will be treated appropriately with further analgesics and withdrawn from the study. Importantly, methoxyflurane should offer greater levels of pain control than the current standard (local anaesthesia alone).

If additional analgesia is requested or required, or if the patient becomes distressed in any way, the patient will be immediately excluded from the main group of the study and treated appropriately. The procedure will be aborted if necessary or additional medication given where needed. We will exclude these patients from the main component of the analysis as this would confound direct comparison of methoxyflurane vs the control but we will include all of these patients in the discussion in order to identify any issues or areas for improvement. This has been rare in clinical practice but would form an important part of the analysis when considering its use longer term.

Adverse reactions

Methoxyflurane is well tolerated and side-effects are rare. Side-effects of methoxyflurane are relatively non-specific, mild and self-limiting in nature, with headache, nausea and vomiting being the most prevalent [9]. Methoxyflurane rarely causes severe or clinically significant sequelae, with negligible changes to the cardiovascular and respiratory function [9]. The risk of these adverse reactions will be mitigated during the procedure by regular observations and the study will be ceased and methoxyflurane removed from the patient if an adverse reaction occurs [9,10]. Participants in this study will be monitored closely with observations of heart rate, oxygen saturations and blood pressure checked every 10 minutes and in accordance with current guidelines. This level of monitoring exceeds that recommended in other settings of approved methoxyflurane use, such as the pre-hospital setting, out-of-hospital setting, dental practice or burns clinics [4,5]. Any other adverse reactions encountered from the administration of methoxyflurane or placebo will be managed as per the hospital protocol to ensure participant's safety. It should be noted that no significant adverse events have been reported with methoxyflurane use in our clinical practice.

Nephrotoxicity

Methoxyflurane found in the Penthrox® inhaler is a gaseous ether that was reported to cause nephrotoxicity at anaesthetic doses, which are over ten times the dose used in the Penthrox® device, but is routinely and safely administered in the unmonitored pre-hospital setting and intra-procedurally [2-6,10]. To minimise the already low risk of transient renal impairment, patients will be screened for renal impairment prior to

any procedure. Any patients with renal impairment (eGFR<60) will be excluded from the study as per current practice.

All efforts will be made to ensure participant privacy and confidentiality is respected, (please see section 7.3).

Radiation safety
All radiation safety guidelines will be adhered to as standard of practice in Liverpool hospital interventional radiology. Enrolment in this study does not affect radiation exposure to staff or participants.

7.3 Confidentiality and Privacy

All data will be stored on two password-protected computers in the Liverpool interventional radiology department, locked in the doctor's office. All patient data will be de-identified and anonymised in order to protect patient privacy. Anonymised data will be coded using a randomly assigned study number and stored separately to the data collection sheet. The separate file will link the key MRN data information and the file will be password protected. Specific patient details or identifiers such as name or ethnicity will not be required for the purposes of this study and will not be used or accessed. Confidentiality will be maintained by limiting access to only a few investigators involved in the project. Hard copy information will be destroyed once stored electronically and all data will be disposed of at the end of the standard retention period (15 years for clinical trial as stipulated by NSW requirements). All information in publication will not be identified by individual cases.

Collected data will be stored securely for the protection of patients' confidentiality. All data will be de-identified minimising the risk of confidentiality breach. All aggregated data will be stored on a SWSLHD network drive only accessible to research investigators listed.

7.4 Data Storage and Record Retention

All data will be stored on two password-protected computers in the Liverpool interventional radiology department, locked in the doctor's office and only authorised personnel will have access to the office which requires key and swipe card access and log in credentials would be required to access the computer. The computer is non-portable, no laptop devices will be used. All hard copy forms will be securely stored in the locked filing cabinet in the interventional radiology office and destroyed once stored electronically. The data will only be accessible to investigators involved in the study. Electronic data will be backed-up to protect against data loss. Patients' details will be anonymised from the data collection sheet. Data security is based on the SWS LHD network security as it will be on a SWS LHD network drive in accordance with the institution's data management protocol. The data will be stored for a minimum of 5 years and disposed of at the end of the standard retention period (15 years for clinical trial as stipulated by NSW requirements).

8. SAFETY REPORTING

ADVERSE EVENT REPORTING
The use of methoxyflurane vs placebo will be reported in accordance with standard of practice in Liverpool hospital. Penthrox® will be used safely in accordance with

TGA and hospital in a controlled environment and monitoring for adverse events will be reported in accordance with departmental and hospital policy. The NHMRC standards for safety reporting have been read and will be adhered to for the duration of the study. Additionally processes for the management of patient safety will be governed by ICH GCP guidelines and local policy and procedures.

9. DATA SAFETY AND MONITORING BOARD

The Interventional radiology data and safety monitoring board (DSMB) will oversee the trial, meeting biannually to assess the safety and efficacy in each study group. The DSMB is composed of two senior interventional radiologists, one diagnostic radiologist, one clinical nurse educator and two senior radiographers. All members of the DSMB are independent, not involved with the study and do not have any conflict of interest. Measures will be in place to minimize any perceived conflict of interest. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational DSMB meetings. At this time, each data element that the DSMB needs to assess will be clearly defined.

Methoxyflurane (Penthrox®) is registered with the TGA registered for self-administration in conscious haemodynamically stable patients, under supervision of personnel trained in its use in monitored patients requiring analgesia for various procedures. All patients in the study will be closely monitored by the proceduralist and delegated nursing staff in addition to the DSMB. All staff involved in the study will have inservice training on the correct and safe administration of Penthrox®. All patients in group (1) and (2) will receive education on the safe use of Penthrox® before their procedure. Given this is a widely used analgesic being used for on-label indications in a monitored and controlled environment that meets and exceeds the requirements set by the manufacturer and the TGA this study carries identical risk to other pre-existing uses of this product. Given this is on-label use of a formulary medication all the procedures for the detection, management, evaluation and reporting adverse events/drug reactions are already in place at Liverpool hospital. This study does not look at the safety of the Penthrox® in procedural analgesia that has already been established [2-6]. This study aims to assess the role of Penthrox® in interventional radiology; and to improve the patient experience with regards to procedural pain, anxiety, recovery and length of stay.

Please see section 10 for early termination protocol.
Please see section 8 for adverse event reporting.
Please see section 7.3 for the privacy protection protocol.

10. EARLY TERMINATION

Methoxyflurane (Penthrox®) is already used in clinical practice, and has been regularly used in the interventional radiology department for the last 2 years. There have been no issues or concerns with safety. In addition, it is used in other departments in Liverpool hospital, interstate and in other countries without significant adverse events. Nonetheless, data (including adverse) will be collected and regularly reviewed for quality assurance, and the study would be terminated in the unlikely event that there were any concerns for patient safety.

11. BLINDING AND UNBLINDING

Randomisation will be predetermined and generated by a randomisation engine (randomizer.org) in order to allocate participants into two groups, either methoxyflurane or placebo. The results will be stored securely in sealed envelopes in the interventional radiology department, consecutively numbered and only accessible to the clinical nurse educator/study nurse. Once a patient is assessed and enrolled at the time of consent, the envelope will be opened revealing the allocated study group only to the study nurse. The proceduralist, assistants, scrub and scout nurses, sedation nurse and patient will be blinded to the process and the study group. The placebo (empty training whistle) will be provided to the patient with a few drops of methoxyflurane on the wrist-strap to mimic the characteristic smell and the patient will be instructed to use the medication as clinically indicated.

12. CONFLICT OF INTEREST

There are no conflicts of interest. No sponsorship has been requested nor required. The investigators do not stand to benefit financially or otherwise from the outcomes of the study.

13. FUNDING

There are no financial disclosures.

No funding has been requested nor is required for this project. All investigators are contributing their support willingly and voluntarily in their own time. The MDI company have agreed to supply the training whistles used for the placebo.

14. RESEARCH OUTCOMES

There is no intention to return results or feedback to research participants on completion of the study unless required for safety reporting. Research outcomes will however inform future clinical practice. Potential uses of this de-identified data at the end of the project include publication to share insights gained from this study. Given Liverpool interventional radiology departments promising pilot study on the role of Penthrox® in interventional procedures the outcomes of this study can inform future practice. The data collected covers a variety of patient experience endpoints and can hence provide various qualitative insights on the role of Penthrox® in interventional radiology procedure.

We will aim to publish the research in a peer reviewed journal such as CardioVascular and Interventional Radiology or Journal of Vascular and Interventional Radiology. We can also use the results to guide best practice in our department, potentially using methoxyflurane more or less or in certain circumstances, as clinically appropriate. The data will be archived on two password-protected computers in the interventional radiology department and deleted at the end of the standard retention period. There are no plans to perform secondary analysis on the data at this stage. There are no plans to share the data in the future. There are no contractual obligations or other agreements with any sponsors/funders/other parties that would influence publication or sharing of the data.

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