**Ethics Application**

1. **Title**: Cone beam Computed Tomography guided radial Endobronchial Ultrasound (EBUS) for the diagnosis of Peripheral Pulmonary lesions.
2. **Sponsor name:** University of Adelaide
3. **Investigator details** :

**Principal Investigator (University of Adelaide)**

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Dr Michael Brown is completing a Masters of Philosophy at the University of Adelaide. This project will contribute to his Masters of Philosophy qualification. The results of this project will be cited in the thesis. Michael Brown will operate within the capacity of the University of Adelaide Masters of Philosophy candidate for the duration of the project.

**Principal Investigator (Central Adelaide Local Health Network)**

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1. **Introduction:**

This is a prospective trial of a novel diagnostic method for challenging pulmonary nodules, which includes lung cancers. Currently, pulmonary nodules are biopsied using radial endobronchial ultrasound (EBUS), in-which a bronchoscope is inserted through the vocal cords and into the lungs. A small spinning ultrasound probe is inserted along the working channel of the bronchoscope. The ultrasound is used to identify the target pulmonary nodule. Forceps are then inserted through the working channel and under 2D fluoroscopic guidance the lesion is biopsied. The yield of this process is limited. Our project employs 3D-imaging guidance using a CT Cone beam, which will confirm navigational accuracy by demonstrating diagnostic sampling tools (i.e. the forceps) are in the lesion improving diagnostic accuracy. We will trial this 3D guided technique to assess its role alongside the standard of care. By improving the diagnostic technique of radial EBUS we aim to facilitate a more accurate and more timely diagnosis of lung cancer.

1. **Background**

Peripheral pulmonary nodules (PPNs) are focal parenchymal opacities typically identified on chest imaging. By definition, PPN’s are completely surrounded by pulmonary parenchyma and cannot be visualised endobronchially during bronchoscopic examination[1]. The only definitive method of characterising the lesion is to take a biopsy. The American College of Chest Physicians (ACCP) clinical practice guideline for the evaluation and management of lung cancer recommends using the least invasive diagnostic procedure which would offer both diagnosis and staging in suspected lung cancer [2].

Balancing the least invasive method of diagnosis against optimising and maximising diagnostic yield has been a long standing and challenging problem. Transbronchial biopsy under Fluoroscopic guidance has been the generally accepted method for diagnosing PPNs since the early 1970’s [3].

Studies have identified superior diagnostic yield of radial EBUS when compared to conventional transbronchial biopsy [4]. However, in spite of this, diagnostic yield appears to have plateaued. Meta-analysis and systematic review [5] suggest that the diagnostic yield of traditional radial EBUS Is 71.1%-73% [5, 6]. Other studies however, including registry data, suggests that this may in fact be lower in the realms of 39-57% [7-9]. Proposed limitations to successful radial EBUS biopsy includes the lack of real-time visualization of the sampling process. The removal of the EBUS probe and subsequent reliance on 2D fluoroscopy imaging to determine the success of a biopsy has clear limitation. A number of lesional characteristics also play a role in determining diagnostic yield. The yield of small lesions <2cm have low yields ranging from 11-42% where as lesions >3cm in size can be closer to 92% [1]. Peripheral location of the lesion may also improve the chance of successful diagnosis [10]. Cases in which the probe is located within the lesion had a significantly higher yield (83-87%) compared to when the probe is located adjacent to it (42%-61%) [11, 12]. The presence of a bronchus sign in which a bronchus is seen extending to the lesion on the diagnostic CT has also been a useful predictor for a successful diagnosis [13].

At the Royal Adelaide Hospital, our own internal audit of radial EBUS procedures done by the co-investigators for this trial has demonstrated a diagnostic rate of 73.96% (n=71/96) over a 2 year period. This is consistent with international data as described above.

The alternative to radial EBUS for the diagnosis of PPN’s has historically been CT guided transthoracic needle aspirate. Meta-analysis of 48 articles and 10,383 lesions has indicated a diagnostic accuracy of 92.1%. There is a significant rate of morbidity however with a pneumothorax rate of 20.5-25.9% and a 6.9% chest drain insertion rate[14, 15]. There is also the potential to spread malignant cells from the tumour into the pleural cavity and the rare but severe complication of systemic arterial air embolism[16, 17].

In order to improve diagnostic yield novel alternatives and adjuncts to radial EBUS are being developed. Electromagnetic navigational bronchoscopy (ENB) was first described in 2012 [18]. This involves using the reconstruction of a 3D bronchial tree through which an operator can navigate through the virtual endobronchial view. Target lesions and the route to it are mapped in multiple views. The diagnostic yield of ENB is 67-73.9% [19-21] in most trials but has been reported as low as 38% in registry data [8]. The combination of ENB and Radial EBUS with Guide-sheath has been examined prospectively and may increase the diagnostic yield to 82.9-88% [22].

Cone beam computed tomography has been trialed in recent years with a view to improving on the current 2D-fluoroscopy guided radial EBUS. A series of small prospective trials have demonstrated a high navigational accuracy with a yield of 75% – 93%[23-25]. Diagnostic yield from these trials has been slightly lower in the order of 70-83.7% [23-28]. Retrospective data has reported higher diagnostic rates up to 86.7% [29]. No randomised controlled data exists comparing CT cone beam guided radial EBUS to fluoroscopy guided radial EBUS.

Pre-existing data on radiation dosage is documented under the *safety considerations* header below.

**6) Purpose:**

**Aim**: Using a prospective, observational, single arm method we will trial Radial EBUS using 3D guided Computed-Tomography cone beam (CT O’arm). We intend to add to the sparse global literature to provide information about the role of CBCT navigated bronchoscopy alongside the standard of care as well as the safety and feasibility of this diagnostic technique.

**Hypotheses**

**Hypothesis 1:** In patients with peripheral pulmonary lesions, CT cone beam guided radial EBUS will improve navigational accuracy.

**Aim 1:** To determine whether the CBCT (O’arm)improves the navigation and localisation of peripheral pulmonary lesions.

**Hypothesis 2:** In patients with peripheral pulmonary lesions, CT cone beam guided radial EBUS will have diagnostic accuracy consistent with or superior to fluoroscopy guided radial EBUS as quoted in the literature.

**Aim 2:** to record the histopathological diagnosis for Cone-Beam CT guided radial EBUS

**Hypothesis 3:** In patients with peripheral pulmonary lesions, CT cone beam guided radial EBUS will be a safe diagnostic method comparable to the standard of care (fluoroscopy guided radial EBUS).

**Aim 3:** To record all complications for CT cone beam guided radial EBUS at the completion of the procedure. This will include radiation doses from the CT Cone-beam procedure

Aim 4: To describe the procedural and anaesthetic duration of using a CT O’arm for the diagnosis of peripheral pulmonary lesions

**7) Study Design**

Anticipated start date: February 1st 2023

Anticipated data collection finish date: February 1st 2024

Anticipated finish date: February 1st 2025 (writing and publishing)

1. Participants: n= 50 as an initial pilot and feasibility study of using the MedTronic O-arm

Inclusion criteria

Patients referred to the lung cancer clinic with a peripheral pulmonary lesion that requires a histological diagnosis. Lung nodules with both a high and low pre-test probability of malignancy will be included. Patients will only be included if radial EBUS is the required diagnostic procedure (as opposed to linear EBUS, CT guided biopsy or endobronchial biopsy)

Exclusion criteria

Patients will be excluded if they are unable to give consent, pregnant or likely to be pregnant at the time of recruitment or they are less than 18 years of age

1. Recruitment

Pre-screening processes used to identify eligible participants. Professor Phan Nguyen (Principal Investigator within CALHN) does all lung nodule triaging and is responsible for coordinating the lung cancer clinics with Arash Badiei. The trigger for identifying a possible trial candidate will come at the time of triage or in the lung cancer clinic at first review for any patient that has a lung nodule that requires biopsy with radial EBUS. Under the supervision of Professor Phan Nguyen patients will be approached during this clinic session or directly after their clinic session to discuss the trial.

The patient will be given 24hrs to 1 week to consider participation. They will not be given longer as biopsy of a potential lung cancer is a matter of clinical urgency and delaying the procedure longer would cause unnecessary risk to the patient. This is the standard amount of time that patients typically have between meeting a treating lung cancer specialist and their diagnostic procedure.

The information given to the patient is included in the patient information sheet. They will be educated on the standard approach to peripheral pulmonary nodules which is radial EBUS with fluoroscopy guidance and they will be aware of the limitation in diagnostic yield (this is standard of care counselling. All patients are counselled on the possibility of a non-diagnostic result). They will also have explained to them this alternate method of biopsy using CT cone beam guidance. They will have explained to them the radiation risk and dose and the possible navigation and diagnostic yield benefit. They will then be allowed to consider their options.

Dr Michael Brown, Professor Phan Nguyen, A/Prof Arash Badiei will explain the research project to the patients and any of these investigators will obtain consent.

Consent will be documented in the form of a signature on the consent form.

We intend to recruit 50 participants total.

1. Methodology

A prospective study will be performed of patients undergoing radial EBUS sampling of a peripheral pulmonary lesion. For those patients who consent to participate in the study, they will receive radial EBUS with Cone Beam/O’arm CT guidance. All procedures will be performed in the bronchoscopy suite at the Royal Adelaide Hospital. Bronchoscopies are conventionally performed with administration of either local sedation (intravenous midazolam and fentanyl) or general anaesthetic). Cone beam CT guided biopsies will be performed on a general anaesthetic list.

Procedural technique for Cone beam CT

1. General anaesthesia
2. Mapped using kurimoto bronchial mapping method[35].
3. Flexible fibre-optic bronchoscope inserted through Endotracheal tube
4. Lesion localised by following the map (created in step 2) and using an endobronchial ultrasound probe through a guidesheath
5. 2x Doctor consensus of adequacy and accuracy of radial EBUS navigation (Concentric, eccentric, not visualised).
	1. This process of navigation will be videoed using existing Vendor Neutral archive (VNA) as proof of effort of navigation. Recording bronchoscopy on the VNA is part of standard of care (VNA is a pre-existing SA health network program that is secure and password protected and only accessible with hospital credentials).
6. CT cone beam O’arm used to confirm the position
	1. Biomedical engineering have produced a bronchoscope holder to keep the scope in place so that staff can stand behind acrylic shielding during the low dose CT acquisition.
	2. Navigational Accuracy recorded as “successful” or “unsuccessful”
	3. Proceduralist may need to adapt or manoeuvre the probe depending on the CT films.
7. Once navigational accuracy has been confirmed, Transbronchial needle biopsy, 2x brushings and 5x forcpes biopsies (standard diagnostic tools) will be taken under II guidance. The Medtronic O-arm is capable of II guidance.
8. Assess for complications e.g. bleeding
9. Guidesheath removed
10. Bronchoscope removed
11. Patient extubated

Kurimoto mapping

P190 bronchoscope + Radial EBUS + Guide sheath

Concentric image

Eccentric image

Not visualised

Cone beam CT image (Using medtronic O’arm) with tool in lesion

No change to position (Navigation successful)

Change to position needed (Navigation unsuccessful)

Navigational accuracy based on pre CBCT method

Sampling of pulmonary lesion

* Using transbronchial needle, forceps, brush

Re-navigation using R-EBUS, fluoroscopy and CBCT

Navigation successful

Navigation unsuccessful

Navigational accuracy post CBCT

Sampling of pulmonary lesion

* Using transbronchial needle, forceps, brush

Ionising radiation procedural aspects

The procedure will use a CT O’arm to confirm the presence of the radial endobronchial ultrasound probe within the lesion. The CT O’arm is a Medtronic O’arm O2 Imaging system and this will be the only radioactive source in the procedure. Patients will have 1-2 CT O’arm doses per procedure and the procedure will occur as a once off only. Patients will not have a repeat bronchoscopy with this technique. Once a tissue diagnosis is confirmed patients will proceed with standard practice (surgical referral, medical oncology referral, radiation oncology referral). The procedure will be carried out in the bronchoscopy suites on level 4B of the Royal Adelaide Hospital. The procedure that is standard of care is Radial EBUS under fluorosocopy guidance only. The procedure that is research specific is Radial EBUS under CT O’arm guidance

Data collection

* Demographic data will be taken directly from the hospital Electronic recording system

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| --- | --- |
| Name/description of data | RAH electronic medical records |
| Data custodian | CALHN |
| Database name | Sunrise |
| Agency Type | State |
| Data collection format | Identifiable  |

Pulmonary nodule characteristics (size, location, distance from pleura, Bronchus sign) will be taken directly from the diagnostic CT chest

|  |  |
| --- | --- |
| Name/description of data | Diagnostic imaging services |
| Data custodian | SA Medical imaging, Jones, Bensons, Radiology SA  |
| Database name | SA Medical imaging, Jones, Bensons, Radiology SA |
| Agency Type | State and Private sector  |
| Data collection format | Identifiable  |

Video of bronchoscopic navigation will be recorded using the pre-existing Vendor Neutral Archive (VNA) in the bronchoscopy suite. This is part of the **standard of care** for all bronchoscopy procedures and it is where all images and videos taken in the bronchoscopy suite are stored. The VNA is a SA health network program and all data remains within SA Healths secure network. The VNA is password protected and accessible in hospital only with hospital credentials. This data will not be published and may only be used for independent, blind review (patient data de-identified) by an authorised specialist for future studies.

Intra-operative Data collection will include the length of procedure, post cone-beam CT readjustment manoeuvres required, the radiation dose, navigational accuracy and complications.

Biopsy samples will be collected at time of procedure and sent to SA pathology as is current standard practice. No additional biopsies outside of routine standard of care will be taken. All processing of samples will be routine (the difference will be only in the imaging used to guide the procedure. The biopsy taking process (Needle aspirate, forceps and brush) as well as processing with SA pathology will be unchanged between this procedure and the standard of care. Samples will be collected by the principal investigator (Michael Brown) or co-supervisors (Phan Nguyen and Arash Badiei)**.** Biopsy samples will be put into formalin and processed by SA pathology.Consent is sought for these samples prior to the procedure and there are no separate samples being collected for research purposes

Histopathological diagnosis will be taken from the hospital Electronic recording system which is documented by SA pathology. The database for this information will be Sunrise/EPAS. The Sunrise/EPAS database will be accessed by the PI for CALHN who is Professor Phan Nguyen as well as the co-supervisor Arash Badiei. Given Michael Brown is in his University of Adelaide capacity for the duration of this project he will only have access to electronic medical records during the hours that he is employed by CALHN. He will not have access to medical records outside of these hours for research purposes.

Radiation doses for each procedure will be collected from the MedTronic O’arm O2 imaging system following the procedure. Co-Investigators Kyle Harty and Tristan Jones will have access to the dose reports for each individual case in their capacity as radiographers for South Australia Medical Imaging (SAMI). This information will be analysed as part of the safety assessment (see aim 3 and endpoint 3) to ensure that radiation doses are within the range outlined in the Radiation Safety Report. Consent is sought for the dose of radiation outlined in the *patient information and consent form* which aligns with the Radiation Safety Report prior to the procedure.

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| --- | --- |
| Name/description of data | Diagnostic imaging services |
| Data custodian | SA Medical imaging |
| Database name | SA Medical imaging |
| Agency Type | Public sector  |
| Data collection format | Identifiable  |

Endpoints

Primary endpoint

Endpoint 1:Navigational accuracy recorded as a discrete variable for cone beam guided radial EBUS. The pre-CBCT navigational yield will be recorded and compared to the post-CBCT navigational yield.

* Navigational accuracy by subgroups: Small nodules <2cm, bronchus sign present, location (upper vs lower lobe)

Secondary endpoints

Endpoint 2**:** The histopathological diagnosis for cone beam guided radial EBUS

* Diagnostic accuracy by subgroups: Small nodules <2cm, bronchus sign present, location (upper vs lower lobe)

Endpoint 3: Safety of cone beam guided radial EBUS.

* Complications recorded intra-operatively for cone beam guided radial EBUS
* Radiation dose for Cone beam guided radial EBUS cases will be recorded post operatively.

Endpoint 4: Procedural duration

* Recorded as anaesthetic time (time from commencement of induction to completion of procedure)
* Recorded as procedure time (time from scope insertion through ETT to scope removal from ETT)

Statistical analysis

Primary endpoint

Endpoint 1**:** Navigational accuracy for CT Cone beam guided radial EBUS

* Statistical analysis: Descriptive statistics using SPSS
* Statistical analysis will be completed once all patients have been recruited and their procedures completed (at 12 months)

Secondary endpoints

Endpoint 2**:** Histopathologicaldiagnostic accuracy for CT Cone beam guided radial EBUS

* Statistical analysis: Descriptive statistics using SPSS
* Statistical analysis will be completed once all patients have been recruited and their procedures completed (at 12 months)

Endpoint 3:Safety of CT Cone beam guided radial EBUS including procedural complications and radiation dose.

* Statistical analysis: Descriptive statistics using SPSS
* Statistical analysis will be completed once all patients have been recruited and their procedures completed (at 12 months)
* Individual radiation doses will be reviewed throughout the trial period to ensure the radiation doses are within the range outlined in the Radiation Safety Report. Statistical analysis will be completed once all patients have been recruited and their procedures completed (at 12 months).

Endpoint 4: Procedural duration and anaesthetic duration

* Statistical analysis: Descriptive statistics
* Statistical analysis will be completed once all patients have been recruited and their procedures completed (at 12 months)
1. Patient withdrawal

Patient’s are free to withdraw from the Study at any time. Withdrawal from the study can be achieved by the patient speaking to any of the investigators. Patients will be provided with an additional opportunity to withdraw prior to the procedure when the proceduralist (who will be a co-investigator) reviews the patient in the thoracic bronchoscopy suites.

Should a patient withdraw, their care will revert to the standard of care which is radial EBUS under fluoroscopy guidance.

Data collected prior to the withdrawal will include demographic data and CT data. This information is already part of the standard of care in that treating physicians review demographics and the baseline chest CT as part of routine practice. This data will be deleted from the data collection sheet.

There will be no other impact on this patient’s care.

**8) Roles of individual investigators**

Dr Michael Brown MBBS

University of Adelaide Masters of Philosophy Candidate.

* Principal investigator working in his capacity at the University of Adelaide
* Patient selection
* Patient enrolment and consent
* Proceduralist and collection of biopsies (Michael is the Interventional Pulmonology Fellow at the Royal Adelaide Hospital)
* Manuscript writing
* Dr Michael Brown is completing a Masters of Philosophy at the University of Adelaide. The results of this project will be cited in the thesis.

Prof Phan Nguyen MBBS, PhD, FRACP

Thoracic Physician

* Principal investigator for CALHN and supervisor of Dr Michael Brown M. Philosophy
* Patient selection
* Patient enrolment and consent (Professor Nguyen runs a weekly lung cancer clinic at the RAH)
* Data collection and access of EPAS/Sunrise
* Proceduralist and collection of biopsies (Professor Nguyen is an Interventional pulmonology consultant at the Royal Adelaide Hospital)
* Editor of manuscript

A/Prof Arash Badiei MBBS, FRACP

Thoracic Physician

* Co- investigator working in the capacity of CALHN
* Patient selection
* Patient enrolment and consent (A/Professor Badiei runs a weekly lung cancer clinic at the RAH)
* Data collection and access of EPAS/Sunrise
* Proceduralist and collection of biopsies (A/Prof Badiei is an Interventional pulmonology consultant at the Royal Adelaide Hospital)
* Editor of manuscript

Prof Hubertus Jersmann MBBS, FRACP

Thoracic Physician

* Co- investigator working in the capacity of CALHN
* Patient enrolment and consent
* Proceduralist and collection of biopsies (Professor Jersmann is an Interventional pulmonology consultant at the Royal Adelaide Hospital)
* Editor of manuscript

Dr Chong Ghee Chew MBBS, FRACP, FAANMS

Nuclear Medicine Physician

* Co-investigator working in the capacity of CALHN
* Ensure patient safety from an ionising radiation perspective

Tristan Jones  BMedRad(DiagRadiog)

Head Radiographer – Fluoroscopy and Interventional Radiography

* Co-investigator working in the capacity of CALHN
* Ensure patient safety from an ionising radiation perspective
* Correct implementation of CT O’arm
* Data-collection – specifically for the radiation doses of each Cone Beam CT

Kyle Harty  BMedRad(DiagRadiog)

Supervisor Radiographer – Fluoroscopy and Interventional Radiography

* Co-investigator working in the capacity of CALHN
* Ensure patient safety from an ionising radiation perspective
* Correct implementation of CT O’arm
* Data-collection specifically for the radiation doses of each Cone Beam CT

Mr Benjamin Crouch BSc (Hons), PhM

Medical physicist

* Co-investigator working in the capacity of CALHN
* Medical physics report
* Ensure patient safety from an ionising radiation perspective

**9) Confidentiality and Data security**

Data that will be collected for patients enrolled in this study are demographic data which includes patient name and age. The diagnostic CT will then be analyzed to collect data on nodule size, nodule distance from pleura, the presence of a ‘bronchus sign’ and the location of the nodule within each lung. Procedural data to be collected includes navigational accuracy of the radial EBUS as assessed by the proceduralist and the number of CT cone beams used to confirm the radial EBUS probe is within the lesion (1 or 2 cone beam CTs). The duration of the procedure will be recorded, the radiation dose will be documented and any complications. After the procedure, the histopathological report documented by SA pathology on Sunrise/EPAS will be accessed by the CALHN principal investigator so as to determine the diagnostic yield.

Data collected will be recorded in a password protected Microsoft Excel spreadsheet. Microsoft Excel has been selected as it is the program most familiar to the investigator group. Once enrolled patient data will be de-identified and will only be re-identifiable by a separate study code. This code will be on a separate re-identification log which will also be password protected. This code will be kept separate to the data and will only be available to the primary investigator and primary supervisors (Michael Brown, Phan Nguyen, Arash Badiei). All original and essential documents produced during this study will be retained for a minimum of 15 years post study closure. This includes electronic documentation which will be stored at the University of Adelaide and any hard copy data which will be stored in locked filing cabinets only accessible to the study team. Data will be destroyed after the storage period has been completed. Michael Brown (principal investigator) will be responsible for destroying the data. There are no anticipated harms from the data collection

The collection and management of the data meet the ethical principles of the NHMRC National Statement on Ethical Conduct in Human Research 2007 section 1 in that:There is potential clinical benefit from the findings of this study, the study design is sound and scientifically addresses the hypotheses, the study hypotheses are generated from but not addressed by published data, the study design does not compromise the respect of the participants, the investigators are experienced, qualified and competent in this study’s field of research, the investigators have a commitment to searching for knowledge and understanding, follow recognized principles of research conduct, conduct research honesty an disseminate and communicate results, whether favourable or unfavourable, in ways that permit scrutiny and contribute to public knowledge and understanding. The study is also being conducted in an appropriate facility. The selection, exclusion and inclusion of categories of research participants is fair, and is accurately described in the results of the research.

The process of recruiting participants is fair and completely voluntary and there is no unfair burden of participation in this study on particular groups. There is fair distribution of the benefits of participation in this study and there is no exploitation of participants in the conduct of this study. There is fair access to the benefits of research and the outcomes of this study will be made accessible to participants in a way that is timely and clear. The likely benefit of this study justifies any risks of harm or discomfort to participants and the likely benefit may be to the participants, to the wider community, or to both.

The investigators have designed the study to minimise the risks of harm or discomfort to participants and will clarify for participants the potential benefits and risks of this study and will prioritise the welfare of the participants in the research context. Where there are no likely benefits to participants, the risk to participants will be lower than would be ethically acceptable where there are such likely benefits. Where the risks to participants are no longer justified by the potential benefits of the research, the study will be suspended to allow time to consider whether it should be discontinued or at least modified. This decision may require consultation between investigators, participants, the relevant ethical review body, and the institution. The review body must be notified promptly of such suspension, and of any decisions following it. This study respects human rights which includes adhering to the values of research merit and integrity, justice and beneficence. The study respects the welfare, beliefs, perceptions, customs and cultural heritage, both individual and collective, of the participants. The study respects the privacy, confidentiality and cultural sensitivities of the participants and, where relevant, of their communities. Other than the signing of a consent form for participation, there will be no agreements between the investigators and the participants or their communities. The study respects the rights of the participants making their own decisions.Where participants are unable to make their own decisions or have diminished capacity to do so, the investigators have respect for the participants by empowering the participants where possible and providing for their protection as necessary.

In addition to the above, the data may otherwise be discoverable through processes of law or for assessing compliance with research procedures**.** The participants have a right to access the information collected and stored by us about the participants. The participants also have a right to request that any information with which they disagree be corrected. The participants have a right to ask that any stored data be destroyed but should be aware that data which have already been derived may not be able to be destroyed

A significant safety issue (SSI) is a safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial. An Urgent Safety Measure (USM) is a measure required to be taken in order to eliminate an immediate hazard to a participant’s health or safety. A serious adverse event (SAE) is any untoward medical or psychological occurrence that results in death, is life threatening, requires inpatient hospitalisation or prolongation of existing hospitalization, or results in persistent of significant disability or incapacity. A Suspected Unexpected Serious Adverse Reaction (SUSAR) is an adverse reaction that is both serious and unexpected.

The principal investigator will report all SAEs, any occurrences of congenital anomaly/birth defect arising from any pregnancy of a participant (or partner) and all USMs instigated by the site within 24 hours of becoming aware of the events to CALHN Research Services. The principal investigator will report as specified in the protocol all safety critical events and any additional requested information relating to reported deaths to CALHN Research Services.

The principal investigator will use continuous vigilance to identify and report all SSIs within 72 hours of identification of the event to all approving HRECs and the relevant Research Governance Officers.

The principal investigator will report all SUSAR within 72 hours of identification of the event to the relevant Research Governance Officers.

**10) Publication**

The results will be presented in our continuing education sessions, the thoracic Society Annual Scientific meeting conference and published in a peer review journal.

**11) Ethical considerations**

The benefits of the study to the participant are justified by the aim of this study which is to improve navigational and diagnostic yield of radial EBUS. For particularly challenging pulmonary nodules this technique may lead to an improvement in diagnostic yield and more confidence in ‘negative’ or potentially ‘inconclusive’ results. This technique may also lead to fewer procedures for an individual (no need for repeat bronchoscopy in the instance of possible false negative). To the local community we will see benefit if this technique improves the diagnostic and navigational efficiency of lung cancer diagnosis. To the hospital, if this study is feasible it may lead to fewer ‘repeat’ bronchoscopies and fewer CT transthoracic biopsies which may reduce wait times. Patients may also be diagnosed with greater efficiency resulting in less stress on the lung cancer service and greater hospital.

Risks to the participant include the radiation dose from the use of a CT cone beam as opposed to the current standard which is uni-planar fluoroscopy (see safety considerations below and the attached radiation forms). All patients will sign a written consent form and data will not be identified and the identity of the participants will not be revealed in any scientific presentations or publications. The participants will be managed in a manner that is no different from current practice. The rate of other radial EBUS complications (bleeding, infection, pneumothorax, hypoxia) are not expected to be any different to the standard of care.

The data collected will be securely kept (password protected database) at the University of Adelaide. The data will be accessible to the patients treating doctor as well as co investigators of this study when working in their capacity within CALHN.

Regarding risk mitigation we will attempt to mitigate the radiation dose given to a patient by limiting the number of CT’s per case. We will do this by carefully manually mapping the bronchial anatomy prior to commencing the procedure. We will also cover the patient where appropriate with lead.

There are no conflicts of interest

**12) Consumer and Community engagement**

Nil

**13) Protocol Deviations**

A serious breach is a breach of Good Clinical Practice or the protocol that is likely to affect to a significant degree the safety or rights of a trial participant, or the reliability and robustness of the data generated in the clinical trial. The principal investigator will use continuous vigilance to identify and report any suspected breaches to the sponsor within 72 hours of becoming aware of the event and report any serious breaches confirmed by the sponsor as occurring at the site to their institution (research governance office) within 72 hours of being notified of the serious breach.

**14) Safety Considerations**

**Radiation (see separate radiation documents provided by Medical Physics)**

A number of studies have attempted to quantify this. The radiation dose from Cone beam CT guided radial EBUS lies within the range of 8.6 and 23mSv [23, 27, 29]. Though it has been reported to be as low as 2.0mSv per CBCT run[26].

The Royal Adelaide Hospital respiratory department has used the CT O arm to sample three patients with challenging peripheral pulmonary nodules. The dose of radiation for these individual patients was 4 to 15mSv.

These radiation doses are not dissimilar to other commonly used investigations. The mean effective dose of Cone beam CT guided percutaneous transthoracic needle biopsy for a small lung nodule is 8.6mSv [30, 31]. For cardiac catheterisation the dose is in the order of 11.8 to 14.8mSv [32]. For simple diagnostic CT studies, the overall median effective doses ranged from 2mSv for a routine head CT scan to 31mSv for a multiphase abdomen and pelvis CT scan. For chest CT imaging the range is 8mSv to 22mSv [33]. For low dose CT chest scans, the approximate dose is 2mSv[34].

**Drugs:**

There will be no drugs prescribed or devices offered to the patient as an outcome of this study

**Other**

We do not anticipate any other safety concerns. Standard risks related to radial EBUS including bleeding, infection, pneumothorax and hypoxia are not expected to be any different between the CT cone beam protocol and the standard of care.

**References**

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