**A Study comparing the current imaging method for screening of occupational lung diseases in dust-exposed workers (ILO CXR) with low-dose high resolution computed tomography (LD HRCT)**

**Clinical Trial Protocol, V1**

# INVESTIGATORS

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# INTRODUCTION

Occupational lung diseases are a group of diseases caused by prolonged inhalation of dust, gases and fumes in the work environment. The diagnoses under the occupational lung disease umbrella associated with dust exposure, and relevant to this project, include the pneumoconioses (coal workers’ pneumoconiosis (CWP), mixed dust pneumoconiosis and silicosis), dust-related diffuse fibrosis and chronic obstructive pulmonary disease (emphysema and chronic bronchitis). For over thirty years, it was thought that these occupational lung diseases had essentially been eradicated from Queensland; until 2015 when CWP was re-identified in coal mine workers[1]. This lapse of three decades has resulted in a large gap in knowledge and experience of the medical community in regards to screening, diagnosis and management of occupational lung diseases.

The proposed study will prospectively compare the current imaging method for screening of occupational lung diseases in dust-exposed workers (with chest x-ray (CXR) reported to International Labour Organisation (ILO) standard) with low-dose high resolution computed tomography (LD HRCT). This project will determine the sensitivity of methods of early diagnosis for occupational lung diseases. The proposed study will provide an evidence-base for potential improvements to the current screening process for workers exposed to dust.

It is well established that duration of dust exposure contributes to the likelihood of a worker having dust related lung disease, particularly for pneumoconiosis. This is true for both coal dust and other respirable silica related pneumoconiosis. This study will therefore include workers with at least ten years of dust exposure as they represent the population of workers at highest risk, with coal workers pneumoconiosis described as having a latency of approximately ten years, and therefore the included workers represent those for whom diagnosis has greatest benefit[2]. Both current and former workers will be eligible for inclusion.

Further, this study will not focus on one specific industry, but rather be inclusive of workers with exposure to respirable coal and silicotic dust. The range of industries to which this applies in Queensland is broad, including (but not limited to) those working in coal, hard rock, construction and quarry industries. Together, this ensures the study has the greatest diagnostic benefit to workers who are most vulnerable to disease. The body of work already performed in workers exposed to engineered stone products means that the value in assessing these workers further is more limited compared to the larger, less investigated groups above. Engineered stone-exposed stonemasons will therefore not be included in this study.

This study will recruit Queensland current and former workers who attend for their mandatory health screening assessment (for current workers) and invited health screening (for former workers). The cohort of invited workers includes mine workers (both coal and hard rock), as well as other industry workers exposed to respirable crystalline silica.

These mandatory health assessments occur at least every five years, and always include chest x-ray (CXR) reported to International Labour Organisation (ILO) reporting standards. We will invite workers with at least ten years of occupational dust exposure history who are eligible for inclusion, and who are presenting for these assessments, to participate in this study. Informed consent will be sought to access their screening records and to undergo a low dose (LD) high resolution computed tomography (HRCT) scan for research purposes. The ILO CXR reporting standards include sections on parenchymal changes, pleural changes and other findings (in section 4, such as lung cancer, cardiac enlargement, vascular and bony pathology).

It is already well-established that HRCT is more sensitive than CXR in detection of pneumoconiosis [3]. LD HRCT is a relatively recent technological advance in the computed tomography field. Several small studies have been conducted comparing CXR and LD HRCT for the diagnosis of dust related lung disease internationally, but no Australian evidence is available to inform current screening methods in the industries prevalent in this country [4].

Further, on the background of occupational lung diseases having gone un-identified for many decades until recently, a study based on the current working population is of the utmost importance in informing current screening guidelines – which have undergone significant modifications in the last five years. This is because of the re-identification of CWP in the coal industry, and the increased awareness of silicosis in silica exposed industries. Of particular note, with the recent emergence of engineered stone-associated silicosis in stonemasons, increased emphasis has been placed on the benefits of using LD HRCT for screening of high-risk workers, rather than CXR alone. This has led to some jurisdictions (such as Western Australia) introducing LD HRCT as the screening method of choice for silicosis, despite the lack of robust Australian evidence.

Taken together, in recent years there have been rapid developments in screening guidelines for occupational lung disease, with limited Australian evidence particularly in the large group of workers exposed to coal and other mine dust – a gap the proposed study will assist in filling by directly comparing ILO CXR and LD HRCT in Queensland workers with occupational dust exposure history of at least ten years.

**PROJECT DETAILS**

# Scientific Aim

The aim of the study is to investigate the value of LD HRCT for the screening of occupational lung diseases by prospectively determining the concordance of standard screening imaging (ILO CXR) and LD HRCT, in workers with a ≥10 year history of occupational dust exposure.

# Research Design and Schedule

This study is a prospective, non-randomised, non-blinded comparative study comparing ILO CXR and LD HRCT. This study will involve 500 patients, who will each undergo both an ILO CXR and a LD HRCT scan. The patients will each have at least ten years cumulative occupational dust exposure, and be undergoing a routine occupational health assessment. Patients in this scenario would routinely undergo an ILO CXR for the purposes of screening for occupational lung disease, thus participation in this study requires one intervention outside of standard care (the LD HRCT scan).

Briefly the study schedule is as follows:

1. Local referrers to the occupational lung screening programs will identify patients in their care who meet the inclusion/exclusion criteria. Once identified, the local referrer will explain the study to the patient and obtain their informed consent if the patient would like to participate. Once informed consent has been obtained, the local referrer will provide the patient with a referral to I-MED Radiology for a LD HRCT scan.
2. A chest radiograph will be performed at a provider of the patient’s choice (as per standard care), and reported through the existing CXR screening programs for current and former workers.
3. A LD HRCT scan will be performed at I-MED Radiology, and reported by two accredited radiologists using the International Classification of HRCT for Occupational and Environmental Respiratory Diseases (ICOERD) grading scale, to consensus.
4. Once the ILO CXR and LD HRCT have been reported, a radiologist accredited to report the CXR and LD HRCT scans will compare the two scan reports (and images if required).
5. The reporting radiologist and the patient’s local referrer will discuss the results of the LD HRCT scan if the scan triggers a radiology positive screening result or an unexpected significant incidental finding is identified (following normal good clinical radiological practice).
6. Patients will continue under the care of their local referrer and/or treating medical team, with no further study involvement.

# Primary Objectives

1. Diagnostic accuracy assessment of ILO CXR vs LD HRCT in triggering a radiology positive screening result requiring further investigation; defined as, findings leading to an ILO score of >0/1; and/or classifiable pleural disease; and/or identification of emphysema or interstitial fibrosis.
2. Comparison of CXR and LD HRCT in screening workers for clinically relevant disease, the diagnosis of which may be based on radiological and non-radiological assessment. If the worker subsequently undergoes a HRCT (not low dose) for diagnostic purposes, and/or is given a clinical diagnosis by a physician, this will contribute to the clinical ground truth for positive cases, noting that not all participants will have additional assessment.

# Secondary Objectives

1. Comparison of diagnostic performance of the ILO CXR vs LD HRCT using different thresholds of positivity on the ILO score triggering a positive screening result. For example, using a score of 0/1 as a trigger vs the current standard of 1/0.
2. Diagnostic accuracy assessment of ILO CXR vs LD HRCT in diagnosis of other radiographic findings which trigger further investigation according to the ILO form section 4, including but not limited to, detection of lung nodules (and investigation of possible lung cancer) and acute findings such as collapsed lung, pneumonia, or bony trauma.
3. The final secondary endpoint is the cohort analysis for eventual clinical diagnosis of dust-related and non-dust related disease identified through the ILO CXR and LD HRCT investigations. This will be presented as a population cohort report documenting the prevalence of findings and incidence of identifiable disease. The study will not be powered for the secondary endpoints, and therefore this forms a subset analysis.

# Data Analysis Methods

The trial objectives will be addressed by collection and analysis of the data points below.

Patient characteristics, to be collected on enrolment in the trial:

* Gender
* Age
* Smoking history (current/previous/never smoker)
* Occupational history
  + Tenure
  + Industry

Data points, to be collected for each ILO CXR and LD HRCT scan,

* Overall image quality (grade 1, 2, 3, non-readable)

Data points, to be collected for each ILO CXR:

* ILO grade
* Presence/absence of pleural plaques, calcification
* Presence/absence of other findings (section 4 categories)

Data points, to be collected for each LD HRCT scan:

* ICOERD grade for round nodules (total and grade for each lung zone)
* ICOERD grade for irregular nodules (total and grade for each lung zone)
* ICOERD grade for ground glass (total and grade for each lung zone)
* ICOERD grade for Emphysema (total and grade for each lung zone)
* Presence/absence of other findings relevant to occupational dust exposure

Data points, to be collected following reporting of both ILO CXR and LD HRCT scans, via discussion between the radiologist and local referrer and/or treating medical team, where appropriate – i.e. different grading outcome:

* Did inclusion of the LD HRCT scan in the worker’s screening trigger further investigation not triggered by ILO CXR?
* Was a discrepancy observed between the radiological findings identified?
  + Did the LD HRCT scan result in a different binary screening outcome (positive vs negative screening result)?
* Was the LD HRCT scan considered more diagnostically useful than the ILO CXR?
* Did inclusion of the LD HRCT scan in the health assessment aid in clinical decision making?

This study compares the diagnostic accuracy of ILO CXR with LD HRCT in detection of radiological findings which trigger a radiology positive screening result.

Therefore, the statistics of interest include:

* Sensitivity
* Specificity
* Positive predictive value
* Negative predictive value
* False positive rate
* False negative rate

of the ILO CXR primary and secondary endpoints of:

* ILO grade threshold for screening positivity >0/1
* ILO grade threshold for screening positivity at other chosen thresholds
* Presence/absence of classifiable pleural disease
* Presence/absence of emphysema
* Presence/absence of interstitial fibrosis
* Presence/absence of other findings (section 4 categories)

compared to the radiological ground truth for this study for each participant (and informing the results for the primary endpoint) which is defined as the consensus opinion of two chest radiologists reading the LD HRCT to ICOERD standards.

It is expected that the LD HRCT will identify larger numbers of early disease cases and will therefore serve as the gold standard.

Statistical analysis will be undertaken by an external consulting statistician, to ensure independence in analysis, as well as expertise in interpretation of data and application of appropriate tests.

In the subset of workers who undergo further radiological and/or clinical investigation, a direct comparison of ILO CXR and LD HRCT performance in identifying screening positive cases leading to diagnosis will also be performed.

Descriptive statistics will be used as appropriate, for example when presenting data on patient characteristics such as mean, median and range of patient age, and on other quantitative data.

# PARTICIPANT GROUP

Queensland workers who meet the inclusion/exclusion criteria will be identified by their appropriate referrer and referred for the study LD HRCT scan after providing informed consent. The inclusion/exclusion criteria are as follows:

# Inclusion criteria

* Minimum of 18 years of age
* Work/have worked in Queensland industry (i.e. coal mine, hard rock mine, quarry and other respirable crystalline silica-exposed work)
* Have at least ten years of occupational dust exposure (coal mine dust or respirable crystalline silica)
* Be undergoing an occupational health assessment that includes an ILO CXR

# Exclusion criteria

* Engineered stone-exposed stonemasons or history of exposure to engineered stone products
* Patients with an existing diagnosis of coal workers pneumoconiosis or silicosis
* Patients undergoing ILO CXR for ongoing medical management of disease diagnosed or suspected through previous occupational screening assessment
* Patients with a CT chest study obtained and available to review within the preceding 6 months

# Recruitment Process

Participants in this study will be identified in one of two ways – either via their local referrer during their routine occupational health assessment, or by self-identification through the former worker program. Self-identification of prospective participants is felt to be an important recruitment method in this study to ensure adequate access for these non-current workers, as well as to ensure a realistic representation of the spectrum of disease and vulnerable population in Queensland.

To inform prospective participants of this study, information sheets will be provided to doctors working in areas with a high number of eligible workers. The local program referrer will explain the study to the worker and invite them to participate. Individuals who are identified via their local program referrer will be provided with both an imaging referral for their standard ILO CXR, and a referral for a research LD HRCT, after consent has been obtained.

Any individuals who self-identify for inclusion into the study outside the existing current or former worker programs will be preliminarily screened by the research team. If it is confirmed the individual meets the requirements for this study (appropriate work history with tenure ≥10 years), the research team will arrange review with a local referrer (for current workers) or designated provider (for non-current workers).

# Withdrawal of Consent Process

Participants will be informed of their right to withdraw from participating in the study at any time, and for any reason. Given this study involves medical imaging, the LD HRCT imaging and radiologist reports will not be deleted, even if requested by the participant, given the legal requirements pertaining to the storage of clinical information. This will be made clear to participants on the Patient Information and Consent Form so they are aware that once consent is provided, any imaging and clinical data collected will not be able to be deleted. If a patient does withdraw from the study, any research-specific data can be withdrawn on request, and they can be excluded from study analysis. If a participant does withdraw from the study, they will be discharged back to their appointed medical advisor who will continue management as standard care.

# SCIENTIFIC VALUE

The aim of this study is to prospectively determine whether the LD HRCT provides diagnostic benefit through more sensitive detection of radiological findings which then trigger a screening positive result, in a cohort of dust-exposed workers at risk of occupational lung disease.

The value in this study includes quantification of the existing disease burden in this cohort, which has not previously been recorded on the existing screening diagnostic test of the ILO CXR, but also to document the change (if any) in identified disease when LD HRCT has been performed. This scientific knowledge is the first of its kind. The recent availability of this CT scanner technology has now enabled this study to be performed.

# Benefits and Risks

The primary benefit to the general public from this research is the potential validation of a new gold standard diagnostic imaging modality for the screening and detection of early stage occupational lung disease. For participants, the potential benefit is that the study imaging may offer improved detection of early stage disease, and thus allow for earlier inventions and treatment planning, compared to standard-care imaging (ILO CXR). We note marked advances in the treatment of early occupational lung disease over the last five years, including antifibrinogenic therapies and whole lung lavage. Early detection is important for many reasons, for example, because there is evidence that ceasing dust exposure may minimise disease progression and the development of symptoms, and will allow lifestyle measures such as smoking cessation to occur for overall respiratory health. Further, sensitive detection of disease improves the respiratory health of the working population as a whole, as feedback can be provided in a shorter amount of time and thus influence aspects such as dust control measures in industry – thus avoiding workers being exposed to environments for decades which may be causative to the development of disease.

There is only minor risk to being involved in this study. These include a small amount of radiation from the LD HRCT, which they would otherwise not undergo (noting that radiation dose reduction technology has led to vastly reduced radiation doses over the last five years); minor inconvenience in the increased length of their attendance at a radiology provider site; and privacy concerns associated with being involved in a research study. To manage these, the imaging protocol for the LD HRCT will be standardised across sites, with radiation exposure kept as-low-as reasonably practicable. Realistically, the amount of radiation exposure involved in undergoing a modern LD HRCT is only marginally higher than that in a standard CXR – an amount which results in no measurable negative health impact. Where the patient has opted into the study prior to the imaging visit, both imaging tests will be conducted at the same clinic and in the same visit where logistically possible, in an effort to minimise participant time and travel requirements. Finally, any identified data and imaging files will only be shared as required for clinical care, or for the purposes of conducting the research as described, by authorised persons only, and while meeting all legal, ethical and policy requirements.

Finally, there is a risk of increased medical intervention in workers who are ultimately not diagnosed with disease, with the associated anxiety, and time off work for appointments and travel. It is anticipated that any financial costs to the worker in this medical investigation would be covered as per usual employment scheme rules. Ultimately, the predicted enhanced diagnosis of significant disease is felt to outweigh any risks present in this study.

# DATA STORAGE AND PRIVACY

Standard I-MED Radiology privacy procedures will apply to data collected throughout the course of this study, as appropriate. Strict patient confidentiality will be maintained at all times. All study paperwork will be stored in a locked draw in the secure offices of I-MED Radiology. Research data will be kept for a period of at least 15 years, after which time it will be disposed of via file deletion or confidential waste disposal. All participant data will be handled only by either a) the investigators listed on this protocol during the conduct of the study, or b) staff directly involved in the participant’s medical care. Identifiable participant research data will not be shared outside the study investigators. Minimal, de-identified information, including clinical information will be stored on the secure web-based capture platform.

The platform will be password protected for each unique user. Only the registry investigators will have access to the platform. There will be two different levels of user accounts. Admin level users will have access to special functions such as exporting data, archiving records, and managing users, whereas general users can view and enter data only. Only designated investigators (Dr Catherine Jones, Dr Katrina Kildey and Dr Sepinoud Firouzmand) will have admin-level accounts. They will be responsible for ensuring the accuracy and completeness of all patient entries and documentation. Strict patient confidentiality will be maintained at all times. All analysis will be performed on de-identified data. At the completion of the study, collected data will be exported and stored on I-MED Radiology secure servers. The exported database will be housed on secure servers at I-MED Radiology for at least 15 years from the date of final publication, after which time it will be disposed of via file deletion.

**EXPERIENCE OF INVESTIGATORS**

**Dr Catherine Jones, Principal Investigator**

Dr Catherine Jones is Adjunct Professor in Clinical Imaging Sciences at the University of Sydney, in the Faculty of Medicine and Health. She practises and lives in Brisbane, working as a full-time cardiothoracic radiologist at I-MED Radiology Queensland.

Catherine obtained her B reader qualification from the National Institute of Occupational Safety and Health (NIOSH) from the United States, part of the CDC network in 2017 and revalidated this qualification in 2020. This qualification recognises her ability in thoracic radiology in the setting of pneumoconiosis detection. The importance of pneumoconiosis surveillance, not just in the coal mining industry but in affiliated industry such as the building and civil engineering sectors, is becoming increasingly recognised. Catherine looks forward to making a significant and ongoing contribution to this important health initiative.

Catherine graduated with a bachelor's degree in mathematics and physics at the University of Queensland in 1997, and subsequently from medical school at the University of Queensland in 2001, before undertaking surgical and radiological training in the UK. She then completed a sub-specialty radiology fellowship in Vancouver, Canada, in cardiothoracic radiology. She has completed Board qualifications in Radiology in both the UK and Australia.

Catherine is the radiologist representative at the Resources Medical Advisory Board for the Queensland state government Office of Industrial Relations, has been a member of the medical advisory panel for the Queensland state government coal workers’ pneumoconiosis screening program, and is the occupational lung disease lead for the Australia and New Zealand Society of Thoracic Radiology. She has published a review paper on the CXR and HRCT appearances of occupational lung disease.

Catherine has been involved in a large number of original research projects, including through the Wesley hospital, Monash university and the Baker Institute (Melbourne) where she holds honorary academic positions.

**Dr Katrina Kildey, Study Manager**

Dr Katrina Kildey is a research manager at I-MED Radiology, The Wesley Hospital – a role which entails management of numerous research projects across several areas, including occupational lung diseases. Prior to this position, Katrina was a Senior Research Scientist at Royal Brisbane Hospital Clinical Research Centre, where she led research exploring the immune response in patients undergoing kidney transplant rejection.

Katrina graduated from a Bachelor's degree in applied science with honours from the Queensland University of Technology in 2011. Subsequently she completed a Doctor of Philosophy at the Queensland University of Technology in 2016. Within her PhD studies, which were based at the Research and Development department of the Australian Red Cross Blood Service (now Life Blood), her work focused on genetic factors that influence red blood cell stability to improve transfusion safety. Most notably, her PhD work led to the discovery of a protein not previously known to RBC biology.

Katrina’s combined employment experiences in the settings of academia, not-for-profit and industry provides a diverse research background and skill set which she will bring to this project as study manager

**Sepinoud Firouzmand, Co-investigator**

Dr Firouzmand is the Research Coordinator at I-MED Radiology, The Wesley Hospital. Within this role she oversees and supports research projects undertaken by the Radiologists at The Wesley Hospital, primarily across the areas of interventional radiology and nuclear medicine. Dr Firouzmand is a GPhCregistered Pharmacist and completed her PhD studies at the University of Portsmouth (UK). She has seven years’ experience in delivery and management of innovative clinical research projects. Discovery of novel molecular fingerprints for diagnosis and potential targeted therapy of a debilitating bladder disease is amongst her recent career highlights. She has led an Innovate UK project and filed two patents, published in prestigious journals and newspapers, and obtained several internal and external research grants.

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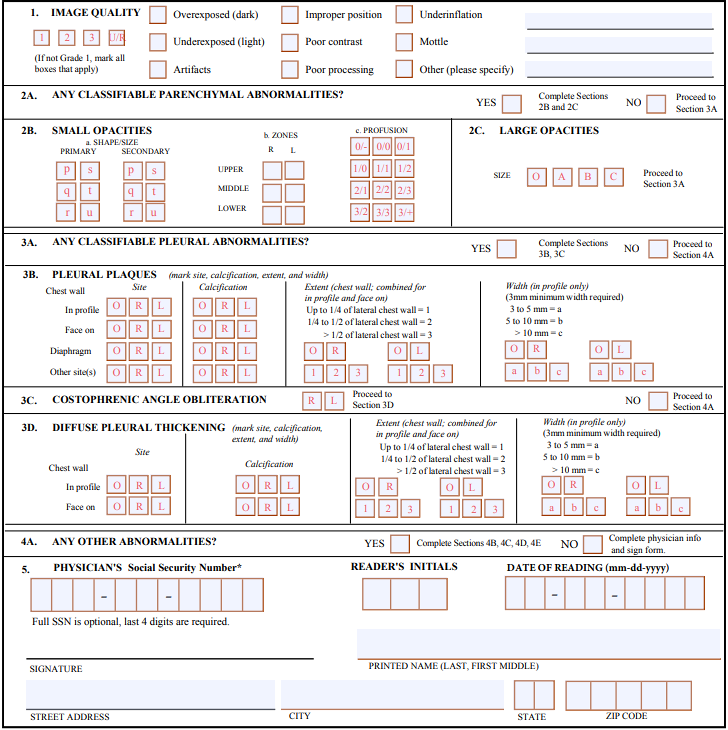
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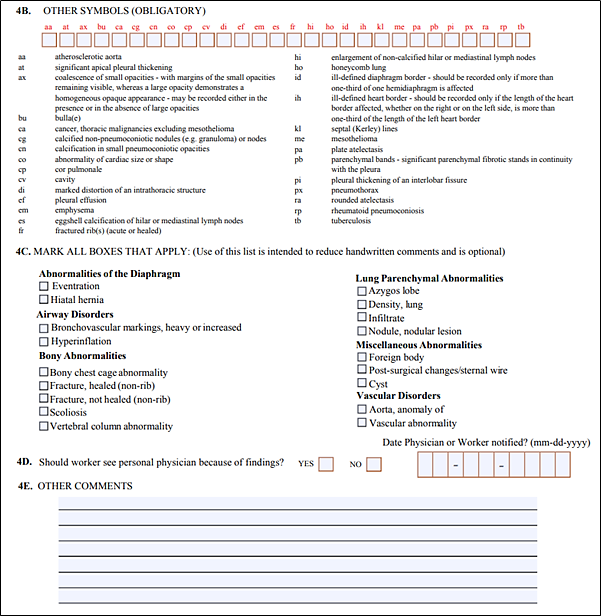
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**APPENDIX 1:** Chest Radiograph Grading System



**Figure 1**: Standard form (page 1) used for grading a chest radiograph for pneumoconiosis within the ILO Classification System of Radiographs of Pneumoconioses



**Figure 2:** Standard form (page 2) used for grading a chest radiograph for pneumoconiosis within the ILO Classification System of Radiographs of Pneumoconioses.