# Study Protocol

## Title of Study :

Rheumatoid interstitial lung disease in Canterbury New Zealand

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## Abstract:

Rheumatoid arthritis **(RA)** is the most common autoimmune joint disease. Improved treatments over recent decades have led to better outcomes in terms of joint damage and disability, and the incidence of several extra-articular manifestations also appears to be decreasing in line with this. Rheumatoid interstitial lung disease **(RA-ILD)** is a serious extra-articular manifestation of RA, and is a notable exception to this trend, with studies showing stable or increased frequency over time. The two most common subtypes of RA-ILD are usual interstitial pneumonia **(UIP)**, and non-specific interstitial pneumonia **(NSIP)**. The aetiopathology of RA-ILD is not completely understood. In addition, management of patients with RA-ILD, including monitoring and predicting which patients will have progressive disease remains a challenge without clear guidelines, and a large amount of research is currently being done in this area internationally. To date there is little known about RA-ILD in New Zealand. The number of persons with RA in Canterbury is also unknown. The overarching aim of this project is to investigate the frequency of RA-ILD in Canterbury, and to determine risk factors and outcomes related to this disease and to compare them to international cohorts.

## Aims:

### Aim 1: To determine the incidence and prevalence of RA in Canterbury New Zealand.

At the present time, the most up to date reliable estimates of the prevalence of RA in New Zealand come from New Zealand Health Survey data, which involve self-reported diagnoses1. Whilst these data provide a useful estimate of disease frequency, they may be prone to self-report and recall bias. Our study aims to improve upon these estimates by using physician diagnosed cases of RA according to validated RA classification criteria.

### Aim 2: To determine the incidence and prevalence of RA-ILD in Canterbury New Zealand.

The frequency of RA-ILD will be determined by identifying cases based upon clinical diagnoses.

### Aim 3: To determine the long-term outcomes of persons with RA-ILD in Canterbury and compare them to international cohorts

We will use clinical data from patient records to determine the rate of progression of radiological and functional investigations, as well as healthcare utilisation, and mortality.

### Aim 4: To determine the risk factors for the development of RA-ILD, and clinical characteristics of individuals with RA-ILD in Canterbury New Zealand.

We will obtain clinical data from all RA-ILD cases and compare them to persons with RA who do not develop RA-ILD, in order to assess the demographic characteristics, disease related factors, and environmental factors associated with the development of RA-ILD.

## Background and significance:

RA is a chronic autoimmune disorder causing joint inflammation and damage, which affects approximately 1% of the population in the United States and Europe2. Having a precise determination of the frequency of RA would be valuable for understanding the burden of this condition in our community, and assist with appropriate planning for the health care needs of patients with RA.

Many patients with RA develop extra-articular manifestations, which lead to significantly increased morbidity and mortality. One of the most serious extra-articular manifestations is ILD. The reported frequency of RA-ILD is variable due to differences in definitions, study design, and the populations analysed. Subclinical disease is more common than symptomatic disease; for example, one group of authors reported a prevalence of clinically significant disease of 14%, compared with 44% who had abnormal findings on clinical investigations (chiefly chest imaging) but no symptoms3. In a USA cohort, the lifetime incidence of clinically significant ILD amongst patients with RA has been reported as 7.7%, leading to an approximately 3-fold increased risk of premature mortality4. The most common radiological pattern of RA-ILD in the Western world is UIP, which comprises approximately 60% of cases5.

To date there is little known about RA-ILD in New Zealand. Aim 2 endeavours to determine a valid and accurate measure of the frequency of this disease, an essential first step in understanding the burden of this condition in New Zealand.

In patients who develop RA-ILD, standardized guidelines for evaluation and monitoring, as well as optimal management are lacking. Many patients have progressive disease not responsive to currently available treatments. Aim 3 will allow greater understanding of the implications that a diagnosis of RA-ILD carries for the individual patient and the health system, and improve care by helping to understand which patients require more frequent monitoring and follow-up.

Aim 4 will add to the current body of international literature regarding risk factors for RA-ILD and has the potential to identify novel risk factors not previously reported. Established demographic risk factors include older age, and male sex. There is very little data regarding ethnicity and the risk of RA-ILD. Disease-specific risk factors include disease duration, radiographic joint damage, and seropositivity for rheumatoid factor and anti-citrullinated protein antibody. Smoking is an established risk factor for both RA, and RA-ILD. Other environmental agents that have been associated with RA include silica, asbestos, mineral oils, pesticides, electronics work, textiles, and roadside dust. None of these have been specifically studied in relation to the development of RA-ILD4,6,7.

This research is of relevance to the New Zealand community, but also internationally. One novel reason for this, not mentioned above, is that the effect of disease modifying anti-rheumatic drugs, **(DMARDs)** have, (if any) on the development and progression of RA-ILD is poorly understood. In New Zealand access to biologic treatments occurred later and the number of biological therapies available is less than in many other parts of the world. Determining RA-ILD frequency and outcomes in the New Zealand context, and comparing them to international data may help to better understand the relevance of DMARDs in the aetiopathogenesis and management of RA-ILD.

This research is intended to form the basis of a larger body of work, investigating RA-ILD in Canterbury. Further work planned for the future includes identifying patients currently attending rheumatology outpatient clinics and undertaking a study of health related quality of life.

## Preliminary Studies:

A recent summer studentship project identified 26 prevalent, and 3 incident cases of RA-ILD in Canterbury in 2006/2007, by screening clinic letters that contained the search term “rheumatoid arthritis”, the Canterbury radiology database for terms ILD or like descriptions in the radiology report and identifying patients with hospital discharge codes for ILD or similar respiratory illness. The number of persons with RA in Canterbury was estimated by combining results for the prevalence of RA from the 2002-2003 New Zealand Health Survey with 2006 census data. The estimated point prevalence of RA-ILD was 5.4 per 100,000 population, and 180 per 100,000 patients with RA. This second figure appears somewhat lower than the rate in some International studies and may be due to an overestimation of the number of people with RA from the New Zealand Health Survey data. 65.5% of cases were female. 97% of case were New Zealand European, and 3% Maori. The mean age at diagnosis was 70.7 (+/-7.7) years. The disease was severe, and the prognosis was poor. 37.9% required home oxygen during the course of the disease. 5-year survival was 58%. As of 31/12/2018, 12 years after follow-up began, 86% had died.

## Research design and methods:

### Overview:

In order to determine the prevalence and incidence of RA and RA-ILD, we will conduct a retrospective cohort study of persons aged 18 years of age and older in the region of the Canterbury District Health Board **(CDHB)**,between 1/1/2006-31/12/2008 and between 1/1/2011–31/12/2013. We will identify existing as well as incident cases of RA, during these times. From this cohort of patients, we will identify existing as well as incident diagnoses of RA-ILD from 2006 to 30/6/2019. We will compare clinical characteristics and outcomes between patients with RA who do not have ILD and patients with RA-ILD, from 2006 to 30/6/2019.

### Setting:

The CDHB encompasses an area on the East Coast of the South Island of New Zealand from the Kaikoura District in the North, to the Ashburton District in the South, as well as the Chatham Islands. The total population of this region is approximately 558,830 people8. Rheumatology care is provided by rheumatologists located at Christchurch Hospital, and there and a small number of rheumatologists working in the private sector.

### Data Resource:

The records of all people who attended the Christchurch Hospital rheumatology service between 1/1/2006-31/12/2008 and between 1/1/2011–31/12/2013 will be examined. Records from both inpatient and outpatient contact will be reviewed. Data regarding demographics and clinical characteristics will be obtained. These years have been chosen because the hospital clinic letters are archived in such a way as to make them accessible for searching. Medical records for patients treated at private rheumatologists will also be obtained to identify any cases managed in the private sector. As almost all cases of RA are managed by rheumatologists in New Zealand, we feel confident that the number of cases of RA missed using this search will be insignificant. In order to ensure we capture all possible cases of RA-ILD, The Canterbury radiology database will also be searched for patients who had a chest radiograph, or chest or abdominal computed tomography (CT) with ILD or like descriptions commented on in the radiology report, and then those individuals who had ever visited respiratory or rheumatology clinics will be identified.

### Identification of Study Subjects:

### Identifications of cases of RA:

Clinical records will be reviewed to identify individuals who meet the 2010 American College of Rheumatology/European League Against Rheumatism Rheumatoid Arthritis Classification Criteria9.

### Identification of cases of RA-ILD:

No widely accepted classification criteria for RA-ILD exist at present. Therefore, we will adopt the criteria used in a previous study from the USA, which applied clinical data, pulmonary function tests, radiologic studies, and lung biopsies to identify cases of “probable ILD”, and “definite ILD”4:

Probable: CXR/CT chest report consistent with ILD

AND

Treating physician diagnosis of ILD

Definite: Diagnosis of ILD by a respiratory physician

AND 2/3 of:

CXR/CT report consistent with ILD

PFTS show TLC ≤ 80%

Lung biopsy consistent with ILD

### Identification of Outcomes:

Once cases of RA and RA-ILD have been identified, the following data will be recorded:

### Basic data:

**Demographics:** NHI, date of birth, sex/gender, date of last follow-up, status at last follow-up (alive/dead), cause of death (if deceased), ethnicity, occupation at RA and RA-ILD diagnosis. **Exposure history:** asbestos, metals, mould/damp, chemical/gases, birds, dusts/silica, compost/potting mix, farm, Tb, smoking status.

*RA clinical characteristics:*

RA diagnosis date, RA ILD diagnosis date. Status (positive/negative/not available or not done) for the following immunological tests: rheumatoid factor (RF), anti-cyclic citrullinated peptide (Anti-CCP), antinuclear antibody (ANA), anti-neutrophil cytoplasmic antibody (ANCA), CRP. Presence of erosive joint disease. Presence of other extra-articular manifestations of RA including cervical myelopathy, Felty’s syndrome, pericarditis, pleuritic, glomerulonephritis, keratoconjunctivitus sicca, xerostomia, vasculitis, subcutaneous rheumatoid nodules.

*Lung disease characteristics:*

**Specific diagnosis:** Presence of obstructive airways disease, chronic obstructive pulmonary disease (COPD), bronchiectasis, bronchiolitis, cricoarytenoiditis, vocal cord dysfunction, inflammatory tracheal lesions, cryptogenic organising pneumonia (COP)/organising pneumonia (OP)/bronchiolitis obliterans with obstructive pneumonia (BOOP), acute interstitial pneumonitis (AIP)/ diffuse alveolar damage (DAD), desquamative interstitial pneumonitis (DIP), lymphocytic interstitial pneumonitis (LIP), non-specific interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP), interstitial pneumonia not-otherwise specified, drug-related pneumonitis. **Presence of other forms of lung disease:** asbestosis, diffuse alveolar haemorrhage, eosinophilic pneumonia, hypersensitivity pneumonitis, lung cancer, pulmonary hypertension, sarcoidosis, vasculitis. **Treatments:** for RA at any time. RA treatments following diagnosis of RA-ILD until last follow-up. Drugs used for treatment of RA-ILD. **Lung physiology:** need for long-term oxygen therapy, pulmonary function test (PFTs) data at diagnosis of RA-ILD, and follow-up PFTs (forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), FEV1/FVC, total lung capacity (TLC), diffusing capacity for carbon monoxide (DLCO), body mass index(BMI), six-minute walk time and distance. **CT chest findings.** **Lung biopsy findings.** **Cardiac parameters:** New York Heart Association (NYHA) functional class, echocardiographic findings, right heart catheterisation study findings.

All data will be collected and entered by HF, with assistance from an experienced rheumatology research nurse.

### Statistical Analyses and Power:

For aims 1 and 2, the prevalence and incidence of RA and RA-ILD for the two time periods will be calculated using CDHB population data from the 2006 and 2013 New Zealand censuses. Between census dates the population will be estimated using linear interpolation. Prevalence and incidence rates will be age- and sex-adjusted to a standard population (e.g., US 2010) to facilitate comparisons with rates from other populations. The cumulative incidence of RA-ILD amongst patients with RA will also be estimated by reviewing the clinical notes of patients with RA, during longitudinal follow-up. The association between the development of ILD and demographic characteristics (age at RA diagnosis, sex, ethnicity), clinical characteristics (seropositivity for RF, anti-CCP, baseline CRP, radiographic erosions), and environmental exposures (smoking, others if enough information available) will be examined using Cox-proportional hazard models adjusting for age, sex, and smoking status. Hazard ratios and 95% confidence intervals for different risk factors will be calculated.

For aim 3, Kaplan-Meier methods will be used to estimate survival rates for patients with RA-ILD. Generalized linear models with random subject effects will be used to analyse repeated PFT measures over time. Also, Kaplan-Meier methods will be used to estimate time to progression of ILD based on thresholds for PFT measures. Cox models will be used to examine potential predictors for progression of ILD.

## Strengths and Limitations:

The proposed study has a number of strengths. Because the CDHB serves a well-defined population, and there are only a small number of rheumatologists taking care of RA patients in the private sector, our estimates of prevalence and incidence of disease are likely to be accurate, and the number of cases missed very small. In addition, New Zealand represents a unique setting to undertake epidemiological research into RA and RA-ILD, due to differences in access to RA therapy compared to other countries.

The main limitation of our study is the retrospective design. Our study will rely on accurate and complete medical record keeping. Whilst demographic, laboratory, radiology, and pulmonary physiology data will be nearly complete, it is likely that information about environmental exposures will often be incomplete. This may limit our ability to identify and draw conclusions about the magnitude of risk for different exposures for the development RA-ILD. It could also mean that there are confounding factors we are not able to identify.

## Ethical Considerations:

Ethical approval will be obtained from the University of Otago Human Ethics Committee and the study will be registered with Australian New Zealand Clinical Trials Registry (ANZCTR).

### Human Subjects:

This project does not involve experimentation on human subjects. It involves retrospective review of information obtained from medical records. The data will be analysed anonymously. Data on individual patients will not be released, and all results will only be published in aggregate.

### Data Management:

Data will be housed in the Canterbury Rheumatology Immunology Research Group database a secure web based database. Data will be recorded onto a paper case record form and then entered in a timely fashion using the unique study identification number for each participant.

### Data Sharing:

De-identified data will not be made publically available at the conclusion of the trial.

References

1. Ministry of Health. New Zealand Health Survey Annual Data Explorer [Internet]. April 2019; [cited 4 September 2019]. Available from: https://minhealthnz.shinyapps.io/nz-health-survey-2017-18-annual-data-explorer/\_w\_0811ceee/\_w\_595dd34f/#!/home
2. Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. Lancet 2010; 376: 1094-1108.
3. Gabbay E, Tarala R, Will R, et al. Interstitial lung disease in recent onset rheumatoid arthritis. Am J Respir Crit Care Med 1997; 156(2):528-535.
4. Bongartz T, Nannini C, Medina Velasquez YF, et al. Incidence and mortality of interstitial lung disease in rheumatoid arthritis: a population-based study. Arthritis Rheum 2010; 62(6):1583-1591.
5. Doyle TJ, Dellaripa PF. Lung Manifestations in the Rheumatic Diseases. Chest 2017; 152(6): 1283-1295.
6. Saag KG, Kolluri S, Koehnke RK, et al. Rheumatoid arthritis lung disease: determinants of radiographic and physiologic abnormalities. Arthritis Rheum 1996; 39(10):1711-1719.
7. Kelly CA, Saravanan V, Nisar M, et al. Rheumatoid arthritis-related interstitial lung disease: associations, prognostic factors and physiological and radiological characteristics: a large multicentre UK study. Rheumatology (Oxford) 2014; 53(9):1676-1682.
8. CDHB. About Us [Internet]. Christchurch: Canterbury District Health Board; copyright [sited 24/3/2019] <https://www.cdhb.health.nz/about-us/>
9. Aletaha D, Neogi T, Silman AJ. An American College of Rheumatology/European League Against Rheumatism Collaborative Initiative. 2010 Rheumatoid Arthritis Classification Criteria. Arthritis & Rheumatism 2010; 62(9): 2569-2581.