Study Protocol

Full study title:

‘Better tests’ – improving diagnostic accuracy and prognostication in Interstitial Lung Diseases

Short Title /Study Acronym	Better tests for ILD
Sponsor	NHS Tayside
Sponsor ID	3-067-24
Funder	British Pigeon Fanciers Medical Research
Chief Investigator	Dr Mark Spears
IRAS Number	348505
Version Number and Date	V1.0 04/08/25

PROTOCOL APPROVAL

'Better tests for ILD'

Signatures
The undersigned confirm that the following protocol has been agreed and approved by the Sponsor, and that the Chief Investigator agrees to conduct the study in compliance with this approved protocol and will adhere to the principles of GCP, the Sponsor SOPs, and any other applicable regulatory requirements as may be amended from time to time.

Chief Investigator: Mark Spears

Signature	Date

LIST OF ABBREVIATIONS

AE	Adverse Event
CI	Chief Investigator
CNORIS	Clinical Negligence and Other Risks Indemnity Scheme
CRF	Case Report Form
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
ICF	Informed Consent Form
IF	Incidental Findings
ILA	Interstitial lung abnormality
ILD	Interstitial Lung Disease
ISF	Investigator Site File
PI	Principal Investigator
PIS	Patient information sheet
REC	Research Ethics Committee
SAE	Serious Adverse Event
SOP	Standard Operating Procedures
SMF	Study Master File
SMG	Study Management Group
SSC	Study Steering Committee

SUMMARY/SYNOPSIS

Study Title	'Better tests' – improving diagnostic accuracy and prognostication in ILD	
Study Design	Single centre observational cohort study	
Study Population	Active Pigeon Fanciers (cohort 1) Patients with established ILD (cohorts 2 & 3)	
Sample Size	750 in total: • 550 pigeon fanciers • 200 patients with established ILD	
Study duration	5 years from recruitment (maximum)	
	Objectives	Outcome Measures
Primary	• Assess candidate non-invasive tests	• Acceptability to patient • Ease of use by clinicians • Association with subsequent outcomes
Secondary	• Examine molecular pathways of relevance to ILD	• Relationships with development of ILD and subsequent clinical outcomes
Inclusion Criteria	Cohort 1: active pigeon fanciers Cohort 2: patients with established ILD Cohort 3: patients with established ILD and respiratory failure resulting in admission	

1. INTRODUCTION & RATIONALE

Background

Interstitial lung diseases (ILDs) are a common presentation in respiratory clinics, with the fibrosing forms being associated with markedly reduced quality of life, and poor life expectancy. However, despite their condition being one of the common presentations, patients with ILD currently experience a significant delay from presentation to their obtaining a diagnosis or useful treatment, reflecting deficiencies in currently available tests.

When patients present to ILD clinics, clinicians review the available history and physical findings in addition to obtaining lung function, blood tests and high-resolution CT (HRCT) scans. HRCTs are currently the key test in assessment of patients with ILD as they can demonstrate classical changes such as honeycombing, a sign of advanced lung fibrosis and hence poor prognosis. HRCT scan reports are therefore crucial in assessing for suitability for, and access to, anti-fibrotic medication and in decision making around provision of immunosuppression.

However, whilst some HRCT changes correlate well with clinical behaviour and pathological findings on biopsy, it is recognized that HRCT scans have some deficiencies when their position as a key test is considered. For example, there is significant variability in HRCT interpretation. Previous research has demonstrated poor correlation in interpretation of the same scans by different radiologists, with this being evident even when scans are reviewed by highly specialized ILD radiologists (1). In addition to the issue of variability in interpretation, there are also significant gaps in our ability to diagnose and hence prognosticate and guide patients when CT scans show subtle changes known as ‘interstitial lung abnormalities’ (ILAs). ILAs are recognised to contain a group which reflect an early ILD, with 50% of these subsequently progressing to a clinically detectable ILD over several years (2). Currently around 10% of chest CT scans show ILAs (2), which will result in a significant increase in demand for HRCT scans, ILD clinic attendance and monitoring, if appropriate follow up is provided by the NHS using current methods.

Another issue relates to approaches to treatment. Some forms of ILD are associated with good responses to anti-inflammatory treatment (or removal from triggering exposure), whereas others are not. Prediction of response to treatment using HRCT appearance is far from straightforward. Whilst the deficiencies in HRCT interpretation with respect to detection of early ILD and differentiating inflammation from scarring can be overcome using lung biopsies, this is not usually employed in the UK, reflecting concern over morbidity associated with surgery. As a result, patients are commonly observed for a period to detect progression, or offered trials of treatment, without any certainty of useful effect. This situation causes significant distress for patients as they quickly become aware of the prognosis of rapidly progressive fibrosing lung diseases, such as Idiopathic Pulmonary Fibrosis, but are unable to be reassured (or have their concern confirmed).

Finally, it is not uncommon for patients to present de-novo with an ILD causing severe respiratory failure. In this context assessment by CT or lung biopsy is not possible, with medical teams left with significant uncertainty as to the likelihood of beneficial effects from anti-inflammatory treatment. Aggressive anti-inflammatory therapy is provided in this context based on clinician biases towards this approach, with hope of useful effect. This uncertainty, along with significant treatment related side effects and the absence of an ability for clinicians to predict a useful effect from treatment, is grossly unsatisfactory.

Therefore, highly sensitive and specific non-invasive tests that can accurately diagnose early ILDs, allow detection of those with reversible elements, and provide insights into prognosis, are urgently required.

This project aims to improve understanding of the immunomodulatory and environmental drivers of ILD, and to develop non-invasive markers for the detection of progressive ILD and of responses to treatment. We plan to approach this via a series of pilot projects which will assess the potential utility of non-invasive assessments (blood and breath sampling based) to inform future projects in the field of ILD.

We propose to collaborate with Pigeon Fanciers in the initial phases of this project. This group is ideal for assessing tests with the potential to detect early and inflammatory ILD, as Pigeon Fanciers represent a model population at increased risk of developing both inflammatory and fibrotic ILD through repeated exposure to antigenic dust from pigeons. In this group cumulative exposure can be linked to symptoms of relevance and compared to non-invasive tests such as immuno-pathological responses, breath assessments and lung function measurements, and then linked to clinical and radiological changes as they develop. As a result, Pigeon Fanciers provide an ideal cohort to explore pathways associated with the development of ILD to an environmental exposure. In addition, given the tests will be employed at recruitment events at large Pigeon Fancier meetings or on location with Fanciers near their lofts, and hence distant to hospital laboratories, this will allow assessment of the ability of each test to be employed in non-specialist settings, such as primary care, general outpatient areas or community outreach clinics.

Following assessment for potential in this cohort, non-invasive tests that show promise will be utilised in pilot cohorts of patients recruited from ILD clinics, and from those presenting with severe respiratory failure due to ILD within NHS Tayside, to assess their usefulness in well-established disease across the spectrum of presentations.

2. STUDY OBJECTIVES & OUTCOMES

Study objectives

The overall objective of the study is to undertake assessment of candidate non-invasive tests for their ability to predict the presence and evolution of interstitial lung diseases, and clinical behaviours including response to treatment following diagnosis.

Primary objectives:

- Assess candidate non-invasive tests in subjects at risk for ILD (active Pigeon Fanciers) for ability to predict development of ILD
    - Acceptability to participants
    - Ease of use distant to specialist laboratories
    - Relationship between results, symptoms and change in health status and lung function over time
- Assess candidate tests in patients presenting to ILD clinics for
    - Acceptability to patients
    - Ability to detect likelihood of progression in ILD
    - Relationship between test results and response to anti-inflammatory treatment
- Explore candidate tests in patients presenting with severe respiratory failure for
    - Acceptability and potential utility in patients with severe disease
    - Relationship between test results and response to anti-inflammatory treatment

Secondary objectives:

- To improve understanding of the molecular pathways that are affected in development of ILD, to facilitate the identification of novel treatments that can target the relevant pathways.

Table 1: Primary Objectives and Outcome Measures

Primary Objective:	**Outcome Measure:**	**Timepoint of outcome measured**
Assess candidate non-invasive tests	• *Acceptability* • *Ease of use by clinicians* • *Ability to predict subsequent outcomes*	*At time of use, and when events of relevance occur*

Table 2: Secondary Objectives and Outcome Measures

Secondary Objective:	**Outcome Measure:**	**Timepoint of outcome measured**
Assess molecular pathways of relevance to ILD	• *Relationships with development of ILD and clinical outcomes*	*Regularly assessed using available methods*

3. STUDY DESIGN

This project will be an observational prospective, single centre, pilot cohort study, and will comprise three main groups:

- Active Pigeon Fanciers
- Patients attending NHS Tayside ILD clinics
- ILD patients presenting to NHS Tayside hospitals with acute respiratory failure.

Pigeon Fanciers will be recruited at large meetings dedicated to the sport, for example at the Royal Pigeon Racing Association 'Show of the Year' in Blackpool and Scottish Homing Union show in Lanark. From this group a small number will also perform testing before and after undertaking standard husbandry associated with the sport, to assess dynamic change associated with recent exposure.

3.1 INTERVENTION

This study will not deploy any interventions but will undertake non-invasive assessments relevant to lung inflammation and systemic inflammation, e.g. blood or breath samples.

Methods chosen will be utilised based on their likely acceptability to the study subjects, ability to be utilised distant from a specialist laboratory, and according to their availability.

3.2 Investigational plan

Part A – assessment of non-invasive tests in pre-clinical interstitial lung disease

This phase of the project will recruit individuals with regular exposure to pigeons and thereby antigenic dusts to develop a cohort for follow-up.

We will recruit from the Pigeon Fancier community via national and regional pigeon fancier events (for example, The Royal Pigeon Racing Association/British Homing World Show of the Year in Blackpool which attracts 25,000 fanciers each year).

For all individuals who consent to take part in the study, we will assess current clinical characteristics (including immunological sensitisation to pigeon antigens, lung function and respiratory symptoms via questionnaire) and take blood samples for measurement of biomarkers and perform novel breathing assessments. Advice and guidance on best practices to maintain respiratory health will be given to participants.

Participants will be followed annually by a simple yes/no questionnaire (or via subsequent recruitment events) to identify those who have developed new symptoms or signs of interstitial lung disease (ILD). Participants who report that they have consulted their doctor about respiratory symptoms will be contacted to obtain further information, and for those referred to their local hospital respiratory services additional diagnostic information will be requested from their consultant.

The non-invasive assessment data generated will be analysed at baseline, and after each year of follow-up, to identify associations with clinical outcomes (for example, lung function, biomarker profiles, ILD and quality of life questionnaires). Each participant will be followed for a maximum of 5 years from initial recruitment.

Participants (part A) - Active Pigeon Fanciers

Our sampling frame will include individuals who are exposed to pigeons on a regular basis through their activities related to the sport, and by their attendance at national and/or regional pigeon fancier events.

We will recruit individuals across the symptom spectrum, including those who have no symptoms suggesting ILD, individuals who report symptoms suggestive of a response to Pigeon antigen exposure, and those that have a previous ILD diagnosis (prevalent cases).

We expect to recruit 100 individuals at the initial recruitment event at the British Pigeon Racing association show in Blackpool in January 2026 with recruitment of around an additional 100 individuals each year thereafter (at national and/or regional events). These estimates are based on recruitment rates from a previous study.

It is estimated that ~10% of pigeon fanciers experience acute and subacute forms of Pigeon Fanciers' lung and around 0.1% develop chronic fibrotic lung disease (3). Amongst the 550 participants we recruit over the course of the study, we expect around 50 participants to report symptoms of or to be diagnosed with an ILD.

Procedures involving participant contact

At the initial recruitment event, individuals who consent to participate will:

1. Complete a questionnaire with a doctor from the study team. This will obtain information about degree of exposure to pigeons (number kept, hours spent with their birds etc), current symptoms on exposure (including with and without breathing

protection), medical diagnoses including respiratory illnesses and other chronic conditions, and smoking history.
2. Have height and weight recorded.
3. Undergo simple lung function tests (spirometry).
4. Complete additional breathing tests (e.g Oscillometry, 'Breathomics', or other breath collection of potential relevance) as available
5. Provide blood samples (for e.g. neutrophil assays, proteomics and biomarker studies)

All participants will be invited to take part in follow-up at subsequent national and/or regional meetings to allow repeat of available non-invasive assessments and to ascertain if any change in their health has occurred.

Each year, between 6 to 9 months after recruitment, all new and existing participants will receive a reminder/invitation for follow-up at the subsequent meetings and will also be asked if they have experienced any new chest symptoms, been referred to a hospital clinic or had ceased to keep pigeons. Participants will also be provided with a withdrawal form at each contact point, in case this is desired.

A small subset of subjects will also perform testing before and after exposure to their birds, where appropriate, for assessment of the dynamic element of the test under examination (see '*Change over time – assessment of short term responses to exposure'* section below*)*.

Information obtained from hospital/GP records

For participants who report that they have been referred to a Respiratory consultant (either at recruitment or in response to the follow-up questionnaire), diagnostic information will be sought from their primary and secondary care medical records.

A member of the research team will liaise with the participant's GP and consultant to identify the appropriate data-fields (which will include, where available, lung function measures, blood test results, multidisciplinary team (MDT) report, results from CT scan, bronchoalveolar lavage (BAL) results, biopsy results [if undertaken], radiology reports and comorbidities), with information being sent via appropriate secure methods (NHS email for example). An electronic version will be stored securely. Any original paper printouts will be securely destroyed. This information will be used to refine the ILD diagnosis of the individual (for example, to confirm the presence of pulmonary fibrosis). Doctors will be asked to provide the information within 2 months. A reminder will be sent if no response is received within 6 months. Increased awareness of the project will be developed via the British Thoracic Society and Action for Pulmonary Fibrosis, to increase the likelihood of positive responses to our approaching for information.

Individuals who consent to be recruited, but do not wish to have their medical records accessed, individuals for whom medical records cannot be accessed (for example, if the consultants do not reply), and individuals for whom only limited data is available, will still be able to take part and their available data will not be excluded from the study.

Change over time – assessment of short-term responses to exposure

In some subjects the results for candidate tests could be affected by time since exposure to relevant antigens, and therefore useful tests may be excluded from further examination unless this is evaluated.

To explore this aspect, we will again collaborate with Pigeon Fanciers, as their symptoms are well recognised to vary with a relationship to exposure 'dose' and time since exposure. For example, some Pigeon Fanciers develop symptoms only during exposure to their birds, or during certain activities, or several hours after exposure, suggesting a variation in immune and inflammatory pathway responses across the group. These responses may be of relevance to some forms of ILD, and hence the results obtained in clinics, so determination of variation during and post exposure will be crucial.

In a sub-set of participants (around 50 subjects) their tests will be repeated before, during and after exposure to their pigeons, and during different activities associated with caring for their birds. This will be performed at the subject's home, or other site if their Pigeon loft is distant from their home, with subjects who give permission for this additional testing.

Part B – assessment in established interstitial lung disease

Participants will be recruited via ILD clinics, including those at first presentation and with well-established disease, and via patients admitted to hospital with respiratory failure.

Non-invasive tests being examined for potential clinical utility in part A will be performed in this cohort, as able. Repeat measurements over time will be performed with these taking place at clinic attendance or during periods of hospital admission.

Use of the exploratory methods in this cohort with established disease will allow assessment of ease of use from a patients perspective, feasibility for integration into normal clinical processes, and relationship with clinical outcomes (disease label, progression over time, and response to empirical treatment as inflammatory ILD and infection). This will enable an assessment of acceptability and usefulness across a spectrum of disease, and thereby will inform further research projects in this area.

4. Study duration, enrolment and number of sites

4.1 Duration of subject participation

Pigeon fanciers will be followed for a maximum of 5 years from initial enrolment, with yearly contact via either questionnaire or face to face review at Pigeon Fancier meetings.

Participants attending ILD clinics, or admitted with respiratory failure will be followed for 5 years, or death, whichever occurs first.

4.2 Number of sites

This study will be limited to acute sites within NHS Tayside, save for recruitment events for Pigeon Fanciers which will take place at large Pigeon Fancier meetings, for example the RPRA 'Show of the Year'. These events will include a mobile 'research lab', staffed by clinicians and scientists with expertise in the conduct of field research and assessments required for the study.

Assessments performed to examine change over time in Pigeon Fanciers will be conducted at the Fanciers home, or in vicinity of their Pigeon loft (if distant from home).

Design issues and ethical issues that may emerge during the conduct of the study

Success of the project and implications for care of participants

There are not expected to be any implications for care of the participants from the research proposed, with all findings being treated as exploratory until their relationship to treatment responses and clinical behaviour is proven in subsequent appropriately powered clinical research.

Any Pigeon Fanciers who report symptoms suggestive of medical problems at recruitment will be encouraged to speak to their GP or hospital team about issues needing to be addressed (if they have not done so already), with the team providing information on the relevant issue as required to the responsible clinicians.

All fanciers who approach the recruitment team to discuss taking part will be given the opportunity to receive advice from experienced clinicians on how best to reduce their exposure to pigeon antigenic dusts (for example, use of dust masks, improved ventilation in the lofts) whilst still enjoying the sport, given the demonstrated effect of this advice on the management of acute hypersensitivity pneumonitis.

Our findings could advance clinical knowledge of ILD development amongst individuals exposed to pigeon antigens. This could ultimately lead to development of a predictive test to identify individuals who are at highest risk of developing ILD or to new therapeutic approaches to treatment of ILD, the majority of which have unknown causes. If the utilised tests are able to be clearly linked to these outcomes during our project we will inform and appropriately counsel Pigeon Fanciers on how they can reduce their risk of ILD based on the best available knowledge.

We anticipate that our project will provide insights into responses to treatment in patients with life threatening ILD, allowing appropriate powering of definitive clinical research projects. The methods employed will be non-invasive and only performed when patients are able to undertake the required procedures. However the results obtained will not be utilised to direct clinical care, with analysis of findings only taking place after sufficient numbers of patients have undertaken the test, and thereby after conclusion of their admission and completion of treatment.

Risk to subjects:

Blood sampling will be of minimal risk and is less than that taken during regular blood donations so will not cause any symptoms post venesection. The risks to the patient will be the same as that associated with venesection for normal clinical samples by well-trained phlebotomists, namely mild discomfort and bruising. Subjects will be seated to minimise risk if a vasovagal reaction occurs.

Simple lung function testing (spirometry) is non-invasive but is an effort based test and can result in some patients noting dizziness or tiredness. All physicians and lung function technicians involved in the project will be experienced in the performance of lung function tests and the issues associated with population lung screening mitigating any potential risks. Again patients will perform the tests seated and with sufficient time to rest between attempts, to minimise the chance of harm.

When attending recruitment events at large Pigeon Fancier meetings the research team physicians may be asked for advice about ILD and general health and will provide advice; most likely including directing the subject to their GP. For participants who report that they have already been advised by their GP and/or consultant that they have scarring of the lung (severe

ILD), the research physicians will provide appropriate advice (this might include advising the participant to minimise or cease their exposure to pigeons if viewed as appropriate).

The research laboratory team attending recruitment events at large Pigeon Fancier meetings will act appropriately to any medical emergencies and provide first aid on a 'Good Samaritan' basis until emergency service personnel attendance.

Sharing of information with other researchers

To improve research in this area, we may collaborate and thereby share samples, and basic clinical information with *bona fide* researchers in different organisations, including those in other countries or in commercial organisations. Such data will be labelled with a unique number but will not be identified by a name or date of birth. Appropriate Material Transfer Agreements will be put in place prior to any sharing of data. Any use of samples other than by the named researchers will require Ethics Committee approval.

Withdrawal from the project

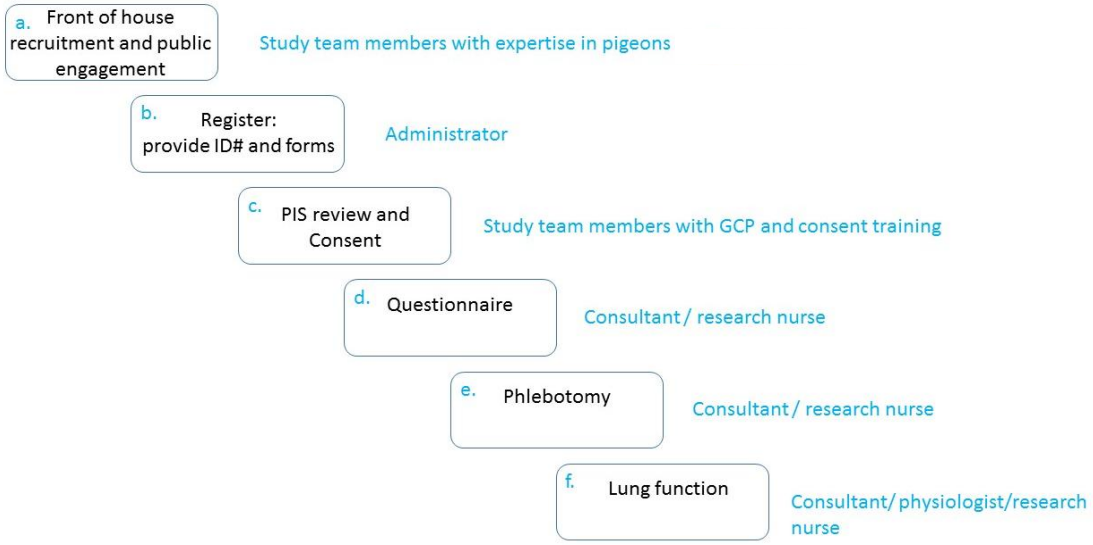
Participants will be free to withdraw from the study at any point. During the consenting process participants will be provided with a withdrawal form that can be sent to the CI notifying their desire to withdraw. At each subsequent point of contact participants will be provided with a withdrawal form to ensure that the opportunity to do so is highlighted again. Participants can also indicate their desire to withdraw via telephone or email to the CI with their being made aware of the options available as per with withdrawal form (as below).

The withdrawal form will provide several options (no further contact but ongoing use of obtained data, withdrawal and removal of all obtained data (before data collection completed for project or before data analysis performed), and request 'to be forgotten' which would result in all personal data is deleted from verification records maintained for this project). Amendments to the withdrawal process will be undertaken as required to ensure alignment to amendments to relevant legislation.

Some patients may lose capacity during the study, and if this occurs their representatives can request their withdrawal from the project on their behalf. If patients lose capacity but we are not asked to withdraw them by their representatives the project will continue to follow them for relevant events (as able) until completion of planned follow up.

4.3 STUDY FLOWCHARTS

4.3.1 Recruitment schema for Pigeon Shows:



Overview of Part A (for those attending recruitment events at large Pigeon Fancier meetings):



4.4 STUDY ASSESSMENTS

Research methods

Breath biomarkers

Non-invasive assessment of signals detectable in breathing tests or via exhaled markers will be employed. These will include novel methods for real time examination of breathing patterns

or metabolites, or collection of exhaled breath for examination for volatile exhaled molecules with later analysis, or other relevant tests.

Breath samples collected at Pigeon Fanciers meetings will be analysed using techniques such as mass spectrometry (through collaboration with specialist groups or relevant companies with this interest), to enable identification of non-invasive breath-based biomarkers that would be easily deployed in the clinic.

'Breath Biopsy' via the ReCIVA® device developed by Owlstone Medical (or similar approaches) will be deployed to collect volatile organic compounds in selected patients, as funding allows. The ReCIVA® device process allows collection of exhaled breath and thereby volatile organic compounds (VOCs) during normal tidal breathing, with collection via the device onto four adsorbent tubes, along with background environmental levels. Subsequent analysis of collected VOCs using gas chromatography mass spectrometry and high field asymmetric waveform ion mobility spectrometry provides detailed unbiased results, which can be linked to subsequent clinical outcomes.

Spirometry will be performed by appropriately trained clinical staff, such as experienced doctors or respiratory physiologists, as per agreed standards (ATS 2019). Subjects will perform the test seated in a relaxed upright position, whilst wearing a nose clip. Appropriate coaching and encouragement with be provided to ensure optimal performance. Test quality of C or better will be accepted for use in future analyses.

Forced Oscillometry Technique to assess airway impedance will be performed as per agreed standards (4), and manufacturers requirements, using the Resmon Pro V3 system. Briefly the subject will be seated, with hands placed on cheeks and with nose clip applied and mouth sealed around the mouthpiece for the device. Ten acceptable tidal breaths will be performed whilst the Resmon Pro V3 collects data on airway reactance and resistance across several frequencies generated by the sinusoidal waves generated by the equipment.

Blood neutrophil responses
Peripheral blood samples will be stored in appropriate media until further processed for assessment of activation status (via cell surface markers), response to stimuli (for example pigeon antigens). Additional 'near patient' testing for neutrophil activation status will be performed as laboratory methods develop.

Antibody analysis
Blood samples will be processed to determine the presence of antibodies of relevance to ILD (ILD clinic panel), which will include specific IgG to Pigeons, fungi, autoantibodies associated with connective tissue diseases and ILD. In addition, the ability of the Fc portion of relevant antibodies to promote inflammatory responses in laboratory models will be assessed, along with examination of the Fc portion for post translational modifications of relevance to stimulation of immune responses.

Inflammatory biomarkers
Blood samples will be processed for subsequent testing using panels of cytokines and chemokines of relevance to inflammatory pathways.

Proteomic measurements
A blood sample will also be processed for subsequent proteomic analysis. This will include measurement of serum levels of a panel of proteins.

Collection and use of participant data and biological specimens in ancillary studies

Excess biological samples that remain after the proposed study assessments may be stored for future research, including commercial research, and may be shared with partners, reflecting their expertise and access to novel testing relevant to the study purpose. Appropriate confidential sharing agreements (e.g. Material Transfer Agreements or other relevant approvals required at that time) will be put in place prior to any sharing of data or materials and no subject identifiable data will be shared with third parties.

Consent will include participants being asked to allow samples to be stored for up to 15 years. Samples will be registered used for submission to ethically approved research tissue banks for future unspecified research held within Tayside and will be registered with Tayside Biorepository.

3.8 INCIDENTAL FINDINGS

As with any research involving further examination or investigations, it is possible that clinical signs or research investigations could provide information about the presence or risk of diseases other than the disorder we aim to study. Therefore, we inform the potential participant of this issue in the Participant information sheet (section entitled " What are the possible disadvantages and risks of taking part?)

Any incidental findings (previously undiagnosed condition) considered to be clinically significant will be reported to the participant's GP and/or consultant by the CI or Site PI, with the consent of the participant.

3.9 STUDY POPULATION

This study will examine non-invasive tests of potential utility in:

- Active Pigeon Fanciers
- Patients attending ILD clinics for management of their interstitial lung disease
- ILD patients presenting acutely to hospital services with severe respiratory failure.

3.10 NUMBER OF PARTICIPANTS

Total number of subjects
Pigeon fanciers joining the study via recruitment events at large Pigeon Fancier meetings will be limited to a maximum of 550 subjects, and for those participating in assessments of the acute effect of exposure to pigeons will be limited to a maximum of 50 subjects.

For patients with ILD (attending hospital clinics and those admitted with respiratory failure) will be limited to a maximum of 200 subjects.

Recruitment to each part of the cohort will stop when these numbers are reached, or 5 years have passed since approvals are obtained.

3.11 INCLUSION CRITERIA

- Subjects will be aged 18 to 90 years of age
- To participate in the part A of this study subjects will have to be active Pigeon Fanciers, willing to undergo follow up as described.
- For those participating in part B subjects will be either attending ILD clinics for management of their interstitial lung disease or will present acutely to hospital services with severe respiratory failure due to ILD.

3.12 EXCLUSION CRITERIA

- Unable to provide consent
- Individuals who are participating in the follow-up phase of another interventional trial, or who are enrolled in an observational study (will be co-enrolled where the CIs of each study agree that it is appropriate).

4. PARTICIPANT SELECTION AND ENROLMENT

4.1 IDENTIFYING PARTICIPANTS

Pigeon fanciers will be enrolled via their attendance at recruitment events at large pigeon fancier meetings, such as the RPRA 'Show of the Year' or Scottish Homing Union show.

ILD patients will be identified by their attendance at ILD clinics or via their admission with respiratory failure to hospital wards in NHS Tayside.

4.2 CONSENTING PARTICIPANTS

The Chief Investigator (CI) retains overall responsibility for the conduct of research, this includes the taking of informed consent of participants. They will ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki.

Participants will be provided with a participant information sheet (PIS) either on site, via post or at clinic appointments. They will be given as much time as they require to decide whether they wish to participate or not. For those attending one of our field events this will be less than twenty four hours, but this is recognised to be standard for this form of recruitment. We will keep to standards relevant to this, with emphasis on withdrawal being a simple process, and a detailed discussion being undertaken as part of consent. In addition, participants will be made aware of when they could next take part, such as the following day (for events where the team are present over two days) or following year.

Only study staff experienced in consenting participants, with valid GCP training, will be delegated this role. Where a participant requests to speak with a physician from the study team the consent process will not be completed until the participant has spoken to the physician and had all their questions answered to their satisfaction.

The ability to withdraw from the study at any point will be emphasised and each participant will be provided with a withdrawal form along with their copy of the consent form and patient information sheet, with instruction on how to return this. They will also be informed of the ability to withdraw from the study by contacting the CI directly using the provided details.

The patient information sheet outlines how patient data will be handled, and processed after being obtained, including how information will be protected through the use of study subject numbers, with the associated personal information being kept separate from data stored for the study. This process will be reinforced by the person taking consent explicitly covering these processes during the consent process. The process will also cover how information may be reviewed by the relevant regulatory authorities, and sponsor representatives undertaking monitoring duties.

For adults who lose capacity their previous wishes will remain legally binding, and this will remain valid unless the protocol changes significantly. We will not request repeat attendance of any participant who has lost capacity, but will record any available clinical outcomes to allow assessment of these with the available study results. The yearly contact questionnaire is sent with a withdrawal form which can be returned by next of kin enabling cessation of contact.

4.3 SCREENING FOR ELIGIBILITY

Pigeon fanciers interested in participating in the project will self-present at research stations at large national meetings for the sport. Those who confirm that they are active pigeon fanciers will be offered a PIS information leaflet and an opportunity to discuss the study.

Identification of potentially eligible participants in NHS Tayside ILD clinics or during admission will take place during normal clinical duties of the CI or local sub-investigators. Those thought to be eligible based on review of available data will be approached by the CI, sub-investigators, or other members of staff with delegated responsibility

4.4 INELIGIBLE AND NON-RECRUITED PARTICIPANTS

Those who show interest (attendance at recruitment stations at Pigeon Fancier shows) or are approached based on available clinical information, and are subsequently noted to not fit the requirements of the project will be thanked for their interest and an explanation will offered for why they cannot participate.

4.5 WITHDRAWAL PROCEDURES

Participants will be contacted yearly to establish if new events have occurred, and to confirm ongoing interest in participation. A withdrawal form will be provided at this point, with a stamp addressed envelope. In addition participants will be reminded that they can communicate their intention to withdraw via email or phone call to the CI.

5. DATA COLLECTION & MANAGEMENT

5.1 DATA COLLECTION

Data will be collected in real time using a specifically designed paper data form with the participant (at recruitment events at Pigeon Fancier meetings) or in a reasonable time frame after consent is obtained using data available from routine clinical care (patients attending clinics or ward admissions).

Each participant will be allocated a study number on entering the study and providing their contact details. This associated data will be saved on a password protected Excel file on a biometrically protected laptop brought to site (Pigeon Fancier meetings) or NHS computer (patients of NHS Tayside).

Data collection will be undertaken by the CI, trained study physicians (Pigeon Fancier meetings), or sub-investigators with relevant training.

Paper data forms completed at Pigeon Fancier recruitment events will be returned to NHS Tayside premises by the CI, with subsequent data entry in Excel completed by the CI. Data transfer (outside of results obtained onsite at Pigeon Fancier meetings) will be via standard post or secure email e.g. NHS mail, for example information sent in response to request for information on new clinical events.

The CI or delegate will maintain source documents for each participant in the study, consisting of hospital medical records containing demographic and medical information, laboratory data, and the results of any other tests or assessments.

Data analysis

Baseline data will include demographics, lung function, relevant exposures or symptoms on exposure (Pigeon Fanciers only) and results obtained from research methods on site at Pigeon Fancier meetings or within NHS Tayside or from subsequent analysis off site.

All blinded data will be collected and reviewed by clinically-trained members of the research team prior to analysis. Variables will be analysed as quantitative, binary or categorical according to the specific research questions being addressed.

All data generated will be linked to a code, enabling anonymisation, and securely stored using methods compatible with NHS and IT requirements. Data will be kept for 10 years to enable completion of analysis.

5.2 DATA MANAGEMENT SYSTEM

Data management will be conducted in compliance with TASC SOPs on Data Management, including TASC SOP Data Management Systems in Clinical Research.

The data management system (DMS) will be Excel, as approved by Sponsor. A study database and case report form (CRF) will be developed according to NHS Tayside SOPs. The database will not collect more information than is required to meet the aims of the study and to ensure the eligibility and safety of the participant. The database will be stored on a NHS Tayside server, with appropriate data protection methods in place.

The DMS will be based on the protocol and CRF for the study and individual requirements of the investigators. The database is managed in line with all applicable principles of medical confidentiality and data laws. The Data Controller will be NHS Tayside and the Data Custodian will be the CI.

The CI may delegate CRF completion but is responsible for completeness, plausibility and consistency of the CRF. Any queries will be resolved by the CI or delegated member of the study team.

Database lock will be conducted in compliance with TASC SOP Locking Clinical Study Databases.

6. STATISTICS AND DATA ANALYSIS

6.1 SAMPLE SIZE CALCULATION

As this study is descriptive and exploratory in nature, with its purpose being assessment of acceptability of tests and potential association of results with subsequent events, no power calculations have been performed.

6.2 PROPOSED ANALYSES

Patient acceptability will be examined through narrative feedback, and visual analogue scales. Association between results will be examined through relevant methods such as correlations and regression analyses.

6.3 MISSING DATA

6.4 TRANSFER OF DATA

No subject identifiable data will be transferred to third parties, with only anonymised data being shared to allow analysis by appropriately skilled team members. This will be shared using

appropriate transfer methods meeting conditions in relevant TASC SOPs and pertinent legislation.

Where data requires to be transferred, an appropriate Data Transfer Agreement will be put in place where required. Agreements will be put in place to ensure relevant methods are employed, with consultation with the sponsor before any transfer of information takes place.

6.5 INSPECTION OF RECORDS

The CI, PIs and all institutions involved in the study will permit study related monitoring, audits, and REC review. The CI agrees to allow the Sponsor or, representatives of the Sponsor, direct access to all study records and source documentation.

7. GOOD CLINICAL PRACTICE

7.1 ETHICAL CONDUCT OF THE STUDY

The study will be conducted in accordance with the principles of good clinical practice (GCP).

In addition to Sponsorship approval, a favourable ethical opinion will be obtained from the appropriate REC and appropriate NHS R&D approval(s) will be obtained prior to commencement of the study.

7.2 CONFIDENTIALITY AND DATA PROTECTION

The CI and study staff will comply with all applicable medical confidentiality and data protection principles and laws with regard to the collection, storage, processing and disclosure of personal data.
The CI and study staff will also comply with the requirements of the General Data Protection Regulation (EU) 2016/679 (GDPR) and the UK Data Protection Act 2018 or any subsequent amendment or replacement thereof with regard to the collection, storage, processing and disclosure of personal data and will uphold the principles of GDPR in Article 5. The CI and study staff will also adhere to the NHS Scotland Code of Practice on Protecting Participant Confidentiality or equivalent.

All study records and personal data will be managed in a manner designed to maintain participant confidentiality. All records, electronic or paper, will be kept in a secure storage area with access limited to appropriate study staff only. Computers used to collate personal data will have limited access measures via user names and passwords.

Personal data concerning health will not be released except as necessary for research purposes including monitoring and auditing by the Sponsor, its designee or regulatory authorities providing that suitable and specific measures to safeguard the rights and interests of participants are in place.

The CI and study staff will not disclose or use for any purpose other than performance of the study, any personal data, record, or other unpublished, confidential information disclosed by those individuals for the purpose of the study. Prior written agreement from the Sponsor will be required for the disclosure of any said confidential information to other parties.

Access to collated personal data relating to participants will be restricted to the CI and appropriate delegated study staff.

Where personal data requires to be transferred, an appropriate Data Transfer Agreement will be put in place.

Published results will not contain any personal data that could allow identification of individual participants.

7.3 INSURANCE AND INDEMNITY

Tayside Health Board is sponsoring this study.

Insurance –
Tayside Health Board will maintain its membership of the Clinical Negligence and Other Risks Insurance Scheme ("CNORIS") which covers the legal liability of Tayside in relation to the study.

Where the study involves University of Dundee staff undertaking clinical research on NHS patients, such staff will hold honorary contracts with Tayside Health Board which means they will have cover under Tayside's membership of the CNORIS scheme.

Indemnity The Sponsor does not provide study participants with indemnity in relation to participation in the Study but has insurance for legal liability as described above.

8. ADVERSE EVENTS

8.1 DEFINITIONS

Adverse Event (AE)	Any untoward medical occurrence in a clinical research participant which does not necessarily have a causal relationship with study participation
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life threatening • requires hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability or incapacity • is a congenital anomaly or birth defect • Or is otherwise considered serious

Worsening of the condition under study will not be classed as an AE, but will be defined as an outcome. Pre-specified outcome(s) will not be classed as an AE but as an outcome.

AEs that occur whilst performing the tests being examined in the study will be recorded as an outcome. SAEs that are related to the tests being examined in the study will be reported in standard fashion, as well as being recorded as an outcome.

As Pigeon Fanciers will attend recruitment events at local and national meetings, with limited subsequent interaction with the team, we may receive reports distant to the event, including hospitalisation. The number of AEs reported to the team are likely to be limited in number as a result. Once the CI is made aware of events qualifying as SAEs from this cohort these will be reported in standard fashion.

The CI will make a clinical judgment as to whether or not an AE is of sufficient severity to require the participant's removal from the study. A participant may also voluntarily withdraw from the study due to what he or she perceives as an intolerable AE. If either of these occurs, the participant should, if required, be offered an end of study assessment and be given appropriate care under medical supervision until symptoms cease, or the condition becomes stable. AEs will be followed up until 30 days after participant's last visit.

The CI or delegate will ask about the occurrence of AEs and SAEs and hospitalisations at every repeat visit during the study. **SAEs which are both unexpected and related to study participation** will be submitted on an HRA NCTIMP Safety Report form to the REC by the CI, within 15 days of becoming aware of the SAE, and copied to the Sponsor Research Governance Office.

9. ANNUAL REPORTING REQUIREMENTS

Annual reporting will be conducted in compliance with TASC SOP 15: Preparing and Submitting Progress and Safety Reports in CTIMPs and Non-CTIMPs, as a condition of sponsorship and as a condition of a favourable opinion from a REC. An HRA Annual Progress Report for NCTIMPs will be prepared and submitted by the CI to REC, and copied to the Sponsor, on the anniversary date of the REC favourable opinion.

10. STUDY CONDUCT RESPONSIBILITIES

10.1 PROTOCOL AMENDMENTS, DEVIATIONS AND BREACHES

The CI will seek approval for any amendments to the Protocol or other study documents from the Sponsor, REC and NHS R&D Office(s). Amendments to the protocol or other study docs will not be implemented without these approvals.

In the event that a CI needs to deviate from the protocol, the nature of and reasons for the deviation will be recorded in the CRF, documented and submitted to the Sponsor as a potential breach report. If this necessitates a subsequent protocol amendment, this will be submitted to the Sponsor for approval and then to the appropriate REC and lead NHS R&D Office for review and approval.

In the event that a serious breach of GCP or protocol is suspected, this will be reported to the Sponsor Governance Office immediately

10.2 STUDY RECORD RETENTION

Archiving of study documents will be for five years after the end of study

10.3 END OF STUDY

The end of study is defined as database lock. The Sponsor and the CI have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the Sponsor and REC within 90 days, or 15 days if the study is terminated prematurely. The CI will ensure that any appropriate follow up is arranged for all participants.

A summary report of the study will be provided to the Sponsor and REC within 1 year of the end of the study.

11. REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

11.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team and their respective employers. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared.

11.2 PUBLICATION

The clinical study report will be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study.

Summaries of results will also be made available to Investigators for dissemination within their clinical areas (where appropriate and according to their discretion).

12. REFERENCES

1. Walsh SLF, Calandriello L, Sverzellati N, Wells AU, Hansell DM. Interobserver agreement for the ATS/ERS/JRS/ALAT criteria for a UIP pattern on CT. 2015 [cited 2024 Oct 14]; Available from: http://thorax.bmj.com/
2. Hwang J, You S, Lee YJ, Sun JS. Prevalence and progression rate of interstitial lung abnormalities detected on thoracic CT: a systematic review and meta-analysis. Eur Radiol. 2024;
3. Cramer C, Schlünssen V, Bendstrup E, Stokholm ZA, Vestergaard JM, Frydenberg M, et al. Risk of hypersensitivity pneumonitis and interstitial lung diseases among pigeon breeders. European Respiratory Journal. 2016 Sep 1;48(3):818–25.
4. King GG, Bates J, Berger KI, Calverley P, de Melo PL, Dellacà RL, et al. Technical standards for respiratory oscillometry. European Respiratory Journal. 2020 Feb 1;55(2).