STUDY PROPOSAL

Global Evaluation of the Interstitial Lung Disease (ILD) Diagnostic Pathway:

Functional & Operational Characterisation (Phase I);
Diagnostic Agreement & Accuracy (Phase II)

Protocol Version 1.0

Study Sponsor

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1. BACKGROUND

1.1 MULTI-DISCIPLINARY TEAM DIAGNOSIS

In 2002, joint guidance from the American and European Thoracic Societies (ATS/ERS) recommended the need for a dynamic, integrated diagnostic process for idiopathic interstitial pneumonia (IIP) in which clinicians, radiologists, and pathologists exchange information and determination the diagnosis via consensus.[1] This multi-disciplinary team (MDT) approach recognised the key roles that clinical features, imaging (high-resolution computed tomography [HRCT])[2-5] and pathology (surgical lung biopsy)[6] all play in establishing a diagnosis and the critical importance of achieving an accurate (and early) diagnosis in lieu of the broad heterogeneity of prognoses across pathologic IIP subsets.[7-14]

A more recent real-world evaluation of the agreement between individual observer and MDT-derived diagnoses of IIP reported substantial differences in diagnosis reached by individual specialists (clinicians, radiologists or pathologist) working in isolation compared with that reached by those working together to reach a consensus.[15]

Diagnostic inputs (information & expert interactions) in the study were introduced in a step-wise manner:[15]

Step 1: expert clinicians and radiologists independently reviewed HRCTs without clinical or pathological information on which to base their (individual) diagnostic decision making
Step 2: Step 1 + inclusion of standardised presentation of clinical information to inform (individual) diagnostic decision making
Step 3: Step 2 + group discussion prior to (individual) diagnostic decision making
Step 4: Step 3 + inclusion of surgical lung biopsy data and addition of pathologist to group discussion prior to (individual) diagnostic decision making
Step 5: Step 4 + diagnosis reached through consensus.

Diagnosis and diagnostic confidence were recorded at each step and inter-rater agreement evaluated within, and across, expert groups at each step. In general, agreement among and between clinicians and radiologists improved when more data (clinical, radiographic, and pathologic) were provided. Importantly, when pathology results were provided to the group, the radiologists were more likely to alter their interpretation than were the clinicians, and the agreement level of clinicians and radiologists with the pathologist consensus diagnosis tended to increase as additional information was provided. Clinicians tended to be more confident than radiologists in the early steps of the evaluation process, although the number of confident diagnoses increased for all observers as more information was provided.

The authors concluded that histopathologic information has the greatest impact on the final diagnosis and that dynamic interaction between clinicians, radiologists, and pathologists improves inter-observer agreement and diagnostic confidence (endorsing the ATS/ERS recommendation).[1,15]

The MDT is therefore considered the “gold standard” in diagnosis of ILD, but experts recognise that the process is not without its limitations and that potential for imprecision exists.

In everyday routine care, pulmonary physicians, radiologists and pathologists can be separated by time, geographic location and different schedules. Such realities of clinical practice can present barriers when trying to pool information and engage multiple specialists in a consensus approach to diagnosis. These challenges are further exacerbated in settings where care is provided outside a designated ILD-center.

There is limited knowledge of the degree (and way) in which the ATS/ERS recommendation to place the MDT at the heart of the ILD diagnostic pathway has been implemented in routine care. Recently work has begun to start to evaluate and characterise features and processes of ILD MDTs, but typically within and across ILD-dedicated centres and in countries with more mature health economies. Little work has been undertaken in more community-based settings and in lower- and middle-income countries where there is wide variation in access to, and distribution of, healthcare.

1.2 ADVANCES IN IPF THERAPEUTICS

Idiopathic pulmonary fibrosis (IPF) is the most common and lethal of the idiopathic interstitial pneumonias. It is estimated to affect between 14–43 people per 100,000, most commonly occurring in those over the age of 50.[16-18]

The disease appears to be driven by abnormal/dysfunctional alveolar epithelial cells that promote fibroblast recruitment and proliferation. The result is scarring of the lung, irreversible loss of function and decreased oxygen to the major organs of the body.[19,20] It has an associated 5-year survival rate from the point of diagnosis of approximately 20%.[21]

Until recently, treatment options for patients with IPF have been limited, primarily focussing on symptom management and palliation. Yet growing understanding of the pathogenesis of the disease over the last two decades has resulted in the development of novel compounds targeted at the mechanisms underlying the disease pathobiology. Indeed in 2014, the European Medicines Association (EMA) in Europe and Food and Drug Administration (FDA) in the USA approved two “first-in-class” compounds (pirfenidone and nintedanib) for the management of IPF.

Both drugs have pleiotropic mechanisms of action and have been shown to slow disease progression and lung function decline in IPF patients with mild to moderate functional impairment. There are also data to suggest they reduce the risk of acute exacerbations, which can lead to hospitalisation and death.

Although this marks an important step forward for IPF management, without the potential to reverse the disease, the arrival of these therapies places increased emphasis on the need for earlier identification and diagnosis of the condition to optimise the potential treatment benefits.

In parallel to such advances in therapeutics, solutions for differentiating ILDs that use bronchoscopy techniques (offering an alternative to invasive surgery lung biopsy) are progressing apace.

Realisation of the full benefit of this emerging management era for IPF is contingent upon optimum use of diagnostic data to inform accurate and early diagnosis.

1.3 COLLABORATION WITH IN THE RESPIRATORY EFFECTIVENESS GROUP

The Respiratory Effectiveness Group (REG) is a global, not-for-profit research and advocacy group set up to raise the quality and profile of real-life respiratory research. Through its expanding network of nearly 300 collaborators working across 40 countries, the group defragments real-life research activities; sets, implements and advocates for the use of consensus research quality standards, and uses real-life research methodologies (both observational studies and pragmatically designed trials) to addresses gaps in the existing respiratory evidence base. The REG works with a wide range of stakeholders to ensure that high-quality real-life evidence is appropriately used to address unmet clinical needs.

A number of working groups drive forward REG's activities. These groups are targeted at speciality areas where real-life research methodologies have particular utility and/or where there are important clinical questions that classical randomised controlled trials (cRCTs) have not (yet) addressed.

As IPF enters a new therapeutic era and there is a need to understand more about the pathway to diagnosis (both in terms of the natural history the disease and the clinical, procedural pathway) there is increasing need to better characterise real-world practice and diagnostic modalities.

In recognition of this, the newly-formed ILD REG Working Group intends to combine the expertise of ILD practitioners with that of REG's experts in real-world methodologies to develop a research-ready network of clinical ILD experts with experience and/or interest in real-life, pragmatic research.

1.4 RESEARCH PLAN – CHARACTERISATION; AGREEMENT; FUTURE VENTURES

The ILD diagnostic pathway characterisation and MDT agreement and accuracy evaluation that is the focus of this document will be part of a package of diagnostic studies led by the REG ILD Working Group. The study will run in parallel to a database characterisation of the primary care path and will also create a global research network for future real-world and pragmatic studies.

1.4.1. Database Characterisation of the Primary Care Path to Diagnosis

Using the UK's primary care Optimum Patient Care Research Database (OPCRD), the study will characterise patterns of primary care healthcare resource utilisation (HRU) in the years leading up to a diagnosis of IPF. Following a design similar to that used by REG in collaboration with the UK Department of Health to characterise the years preceding a diagnosis of chronic obstructive pulmonary disease (COPD),[22] the study will aim to identify common diagnostic and HRU patterns with a view to identifying potential missed diagnostic opportunities ("red flags") that could be used to inform future primary care decision support tools.

1.4.2. Global Characterisation of the diagnostic pathway in ILD

Phase I of the study outlined in this proposal will address important questions about current ILD diagnostic approaches around the world. It will characterise diagnostic practice in previously little-studied regions across a wide range of resource and healthcare settings, and will inform the optimum design of a subsequent ILD MDT agreement study.

1.4.3. Global ILD MDT agreement study

Phase II of the study outlined in this proposal will evaluated diagnostic agreement and accuracy of current diagnostic practices around the world, seeking to establish the implications of current real-world practice and identify opportunities for future improvement.

1.4.4. Future research

This study (1.4.2 & 1.4.3, above) will not create a network of interested ILD investigators (working across a wide range of geographies and healthcare settings) for inclusion in a wide range of future real-world research collaborations and a map of current practice (and implication of different practice approaches) to inform the evaluation of pipeline ILD therapeutic and diagnostic approaches.

2. RESEARCH RATIONALE & OBJECTIVES

2.1. RATIONALE

Therapeutic advances and stratification approaches based on molecular phenotyping are changing the face of IPF management, but full benefit of these advances requires a reliable, accurate diagnostic algorithm.

While the MDT is advocated as the gold standard in ILD diagnosis, knowledge is limited as to true approach to diagnosis and how (indeed if) the “MDT” is interpreted and implemented at a global level.

Prior studies in dedicated-ILD centres in high-income countries demonstrate wide variation in MDT composition and approaches used and that diagnostic agreement within and across specialist groups can vary depending on the level of diagnostic information considered and extent of cross-disciplinary consultation involved. Variation in diagnostic teams and pathways is likely to feature even greater heterogeneity across a wider range of health economies and healthcare settings (ILD-dedicated and non-ILD-dedicated).

2.2. OBJECTIVES

The REG ILD Working Group intend to identify features of ILD MDTs associated with more accurate diagnosis of IPF with a view to improving diagnostic accuracy and patient stratification to optimise treatment outcomes worldwide.

To achieve this ultimate aim, two discrete, sequential research phases are proposed:

1) **Phase I:** A global, standardised, systematic evaluation of the diagnostic process employed by a range of dedicated and non-dedicated ILD centres worldwide.
2) **Phase II:** A global MDT ILD case review and diagnosis study to:
   a. **Phase IIa:** Assess the diagnostic **agreement** across ILD MDTs
   b. **Phase IIb:** Assess the diagnostic **accuracy** of ILD MDTs.

3. PROPOSAL SCOPE

This proposal focuses on the overall scope and principles of the project and focuses in particular on the details of the Phase I global characterization phase. A high-level outline of the intentions for Phase II is included, but the findings of Phase I will be critical to the appropriate design of Phase II, specifically: what constitutes an MDT,

the geographical distribution of participating centres and the case mix (and scope of data provided for each case) for evaluation. A more extensive Phase II proposal will, therefore, be developed in parallel with the findings of Phase I being finalized.

4. GEOGRAPHICAL SCOPE

Building on prior work,[15,23,24] this study will include dedicated and non-dedicated ILD centres and countries within both mature and expanding economies (featuring a wide range of health systems and health infrastructures) across key global regions.

Of particular interest will be features of practice in Brazil, Russia, India and China (the "BRIC" countries) owing to their limited representation in previous studies and large population size.

The study will take an inclusive approach, welcoming responses from all countries and participants involved in the diagnosis of ILD. From an operational feasibility perspective, however, the following continents, countries and proposed lead contacts will be prioritised for inclusion and to drive local/regional data collection:

Table 1. Priority countries for Phase I inclusion

Continent / Region	Country	Proposed Lead Collaborator
Europe	UK	Luca Richeldi (Southampton)
	Italy	Carlo Vancheri (Catania)
	France	Vincent Cottin (Lyon)
	Germany	Jürgen Behr (Munich)
	Greece	Demosthenes Bouros (Athens)
	Russia	Sergey Avdeev (Moscow)
	Scandinavia	Elisabeth Bendstrup (Aarhus, Denmark)
	Belgium	Wim Wuyts (Leuven)
	Netherlands	Jan Grutters (Utrecht)
	Spain / Portugal	Ferran Morell & Maria Molina Molina (Barcelona, Spain)
North America	USA	Kevin Flaherty (Ann Arbor) & Fernando Martinez (New York)
	Canada	Charlene Fell (Calgary) ± Chris Ryerson (Vancouver) ± Martin Kolb (Ontario)
South America	Brazil	Ivan Rosas (Colombia)
	Argentina	
	Chile	
Asia	Japan	Arata Azuma
	China	Zuo Jun Xu (Beijing)
	India	Zarir Udwadia (Bombay)
	Middle East	Carole Youakim (Beirut, Lebanon)
	The Philippines	Camilo Roa, Aileen David-Wang
Australasia	Australia	Tamara Corte (Sydney)
Africa	South Africa	Keertan Dheda (Cape Town)

5. PHASE I: GLOBAL SYSTEMATIC EVALUATION OF ILD DIAGNOSTIC PROCEDURES ACROSS A RANGE OF HEALTHCARE MODALITIES

5.1. PHASE I OBJECTIVES

Phase I of the study will aim to:

- Generate knowledge of the ILD diagnostic process globally (especially in countries/territories where little is currently known).
- Provide valuable insight as to current diagnostic practices to inform the robust design of Phase II.
- Develop a global network of ILD investigators for engagement in Phase II and in future real-life research initiatives.

5.2. DESIGN & METHODOLOGY

An electronic systematic survey format will be used to capture standardized responses across the range of participants / participating centres.

A survey methodology (adapted where appropriate) developed by Veracyte Inc (San Francisco, CA) as part of a recent evaluation of ILD diagnostic processes across a range of centres (ILD centres and community-based practices) in the USA will be used.[1] The Veracyte methodology uses electronic data capture, enabling it to be readily scaled-up for this larger, global study.

As the methodology was developed for a US, English-speaking participant group, it will need to be reviewed for its relevance, suitability and usability within each of the participating countries.

The Study Steering Committee (see Section 7 [Table 1], comprising Investigators from the REG ILD Working Group and additional national leads) will conduct a group review of the methodology and advise on necessary global and local adaptations (e.g. foreign language translations and terminology differences; relevance to local healthcare settings, etc.).

To reduce potential selection bias, lead collaborators within the prioritised countries and regions (see Table 1) will act as data collection “nodes” – providing local expertise on the geographical distribution of diagnostic centres and the weighting of diagnostic case load across centres. Through local consortia, networks and professional links, these data collection nodes will distribute the survey (and curate responses) within their assigned territory.[2]

The intended participant recruitment approach will result in a pragmatic—“strategic-opportunistic”—approach, combining easily-scalable electronic data capture with local expertise to invite responses from a wide and representative range of (ultimately self-selecting) clinics and centres (see Figure 1).

[1] Results of this work will be presented at the Pulmonary Fibrosis Foundation Annual Conference; Washington, USA, 12-14 November 2015. Veracyte have indicated their strong support of sharing their methodology to extend their US-based evaluation to the global scale proposed for this study.

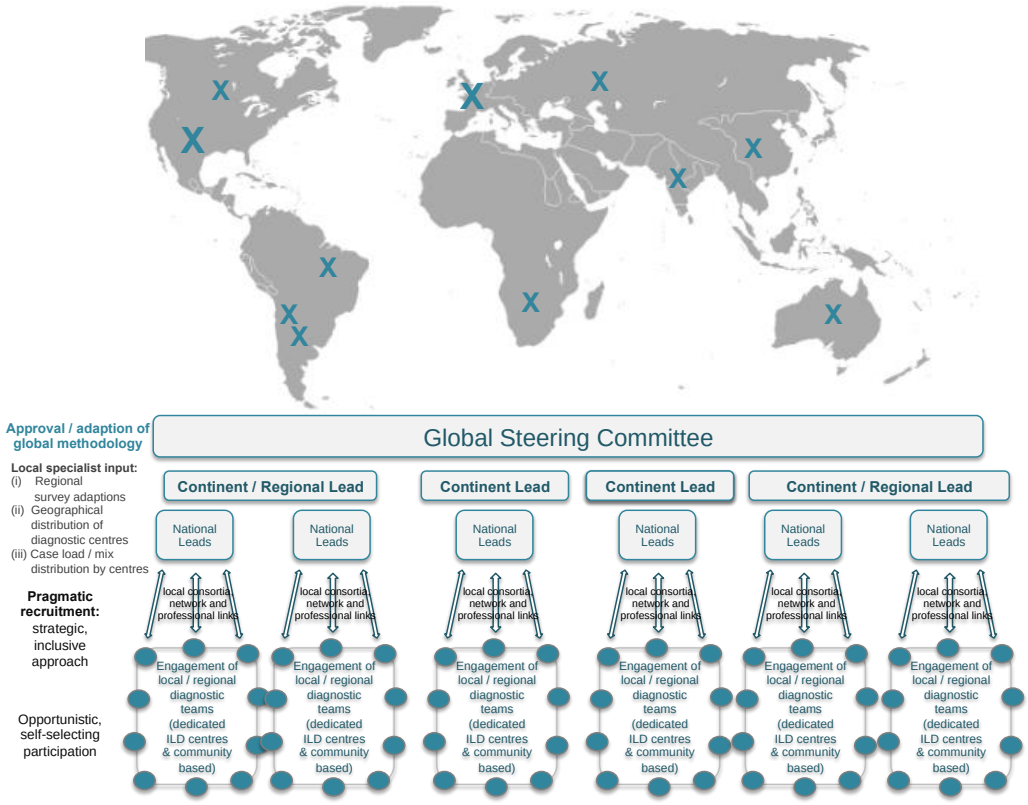
[2] Industry links (see Section 8) and the REG network will be used to engaged appropriate national leads in areas currently “unknown” to the Investigators

5.3. DATA CAPTURE & DATA QUALITY

Utilising electronic case report form (eCRF) technology, data will be captured digitally, stored centrally and monitored at an item, participant, national and regional level, as required.

Edit checks and quality assurance monitoring will be implemented throughout (e.g. requiring data entered to be within logical ranges; designation of mandatory fields that must be completed prior to submission, measurement of survey completion time, data pattern recognition to eliminate respondents seeking to accelerate completion of survey). Features designed to ensure on-going quality and flow/logic questions will also be used, as appropriate (e.g. if answer to question x is 'yes', go to question y). Data cleaning will be conducted and monitored on an on-going basis, enabling remote monitoring of recruitment / participation at a national or regional, as well as overarching, level.

Figure 1. Simplified overview of the survey adaption & dissemination approach



5.4 OUTCOMES

This global e-evaluation of ILD diagnosis will characterise key aspects of the ILD diagnostic pathway and process across the participating centres, capturing:

- Expertise of survey respondent (clinical; pathology; radiology)
- Demographics of respondent site:
  - Geographical territory (continent, country)
  - Practice setting:
    - Dedicated ILD centre / non-dedicated ILD centre
    - Existence of an ILD-focused MDT
    - Academic / community / government practice
  - Diagnostic techniques used in practice
- Patient demographics of respondent site:
  - Number of ILD patients (i) managing and (ii) diagnosing

  - Number of IPF patients (i) managing and (ii) diagnosing
  - Referral pattern of patients (from other centre vs within centre vs direct)
- ILD patient management:
  - Self-managing vs referring to ILD centres
  - Number of physicians seen before current physician
- Approach to diagnosis employed by respondent site:
  - Level of expertise of radiologists / pulmonologists / pathologists used for diagnosis (and where located)
  - Frequency of use of diagnostic tools (CT, HRCT, Bronchoscopy [TBB, BAL, cryobiopsy], Surgical Lung Biopsy) in ILD patients
- Differential diagnosis:
  - Fraction of ILDs by specific disease
  - Confidence of diagnosis at each step of the way (e.g. post HRCT)
- Use of available therapeutics at respondent site:
  - Use and familiarity with available drugs
  - Likelihood of prescribing for patients with varying diagnoses and confidence in diagnosis
- Process of diagnosis:
  - Use of the term “MDT” (Y/N)
  - Method of getting input from other specialists (formal MDT, virtual MDT, informal consults / conversations)
    - If not using MDT:
      - Confidence in diagnostic process
      - Frequency of interactions between specialists
      - Types of specialists consulting
      - Consistency of specialists
    - If using MDTs:
      - Confidence in diagnostic process
      - Fraction of cases that go to MDT
      - Frequency of MDT diagnostic meetings
      - Structure & Format of MDT
      - Attending specialists (clinician, radiologist, pathologist, rheumatology, immunology, thoracic surgeon; transplant physician; palliative care physician; nursing staff; physiotherapy; fellows/registrars; junior trainees; medical students; other)
      - Time per case
      - Diagnostic evaluations available (e.g. HRCT, pathology, clinical information)
      - Case presentation (oral ± audiovisual; all vs. selected investigations)
      - Decision pathway (consensus; discussion + lead specialist decision)
      - Assignation of diagnostic confidence (Y/N)
      - Resolution approaches in the absence of consensus
      - Number of differential diagnoses documented
      - Non-diagnostic information documented by MDT
      - Common diagnostic or management dilemmas discussed.
- New technologies [optional]
  - Likelihood of use of molecular diagnostic test
- Case evaluations: series of cases presented to understand concordance between physicians in study in diagnostic evaluation of ILDs. 4 cases with varying levels of clarity of ILD diagnosis depending on clinical factors and HRCT:
  - Assessment of HRCT
  - Assignment of diagnosis
  - Recommendation of next step for patient (biopsy, drug therapy, waiting)

6. PHASE II: INTERNATIONAL EVALUATION OF DIAGNOSTIC ACCURACY & AGREEMENT ACROSS A RANGE OF SETTINGS REPRESENTATIVE OF REAL-LIFE ILD DIAGNOSTIC PRACTICE

6.1. PHASE II OBJECTIVES

Phase II of the study will aim to:

- Evaluate agreement of ILD MDT diagnosis across a range of global sites and healthcare settings
- Evaluate accuracy of ILD MDT diagnosis across a range of global sites and healthcare settings, considering in particular agreement in IPF diagnosis
- Identify features of current MDT diagnostic practice associated with accurate diagnosis (including the effect of bronchoscopic sampling for diagnosis)
- Produce a series of recommendations as to how best to optimise the pathway to accurate ILD diagnosis in real-world practice.

6.2. DESIGN

To optimize the impact of the study findings and outputs on future guidelines and on future clinical practice recommendations, the study will aim to reflect current practice, in terms of MDT setting (representative involvement of both dedicated and non-dedicated centres); MDT structure/formats/practice (e.g. representative involvement of virtual vs. face-to-face MDTs; pathologist involvement; caseload per meeting, etc.) and MDT case data (e.g. provision of clinical data + radiographic ± pathologic).

In addition, the case mix will be selected to avoid biasing the participants' diagnostic decision making, while also ensuring inclusion of a sufficient number of cases to power an evaluation of agreement across IPF diagnoses.

Appropriate definition of these Phase II design components will be critical to the robustness and relevance of the study. The Phase II definition of an MDT, and the study's geographical scope and case mix distribution, will aim to reflect real-life (as far as is practically possible) as established in Phase I.

6.2.1. MDT definition

ILD diagnostic studies conducted to date have primarily been led by ILD experts working in dedicated ILD centres in largely "idealized" and well-resourced clinical settings. While the internal validity of such studies is robust, their external validity and the ability to extrapolate their findings to the widely heterogeneous range of care settings faced in real-world practice is more limited.

In the absence of a definition of an MDT in the ILD literature, the Phase II definition of an MDT will be informed by the findings of Phase I's inclusive, global characterization of the real-world process. In terms of MDT constitution; format; meeting practice, etc.

6.2.2. Participating Collaborators and Centres

Phase I will generate a cross-sectional "map" of where (as well as how) ILD diagnoses are made around the world, including indicative number, location (rural vs urban) and setting (e.g. community vs dedicated centre) of diagnosing teams and clinicians. Phase II's design will aim to reflect the real-world scenario by weighting participation (and potentially reference case sourcing), as appropriate and feasible, across collaborating countries.

6.2.4. Reference cases

The selection of cases will aim to minimise selection bias and potential confounding of agreement and accuracy outcomes of the study, while aiming to retain sufficient power to evaluate outcomes for the IPF subgroup, specifically. The range and mix of cases required to optimize this goal will be informed by the Phase I characterization of current practice and case mix, but important considerations and possibilities include:

- "**Enriched by fibrotic case load"[3]:** Including a substantial number of progressive fibrotic cases, such as a case composition featuring ~50% IPF cases and 50% (combined) mix of chronic hypersensitivity pneumonitis (HP); nonspecific interstitial pneumonia (NSIP) or unclassifiable ILD, to ensure sufficient power in a subanalysis of IPF cases alone.
- **Availability of follow-up data:** requesting a random selection of cases (within pre-determined case categories, see above) over a pre-specified time period over deemed reflective of current practice (e.g. last 5 years) with associated follow-up data to serve as a objective marker of accuracy of the assigned diagnosis (see below).

6.2.5. Diagnostic "Accuracy"

In addition to evaluating level of agreement between centres, the study will explore the accuracy of diagnosis within each centre and the association between MDT operational features and the accuracy of their diagnostic decision making.

Accurate diagnosis cannot be defined in absolute terms; however, for the purposes of the study diagnostic "accuracy" may be defined in three ways.

Primary definition

Tier 1 "gold standard": an accurate diagnosis will be defined as a ***"diagnosis that agrees with the diagnosis assigned by the source/providing MDT"*** for each case, i.e. the diagnosis as assigned by the local diagnostic team.

Secondary definitions for sensitivity analysis

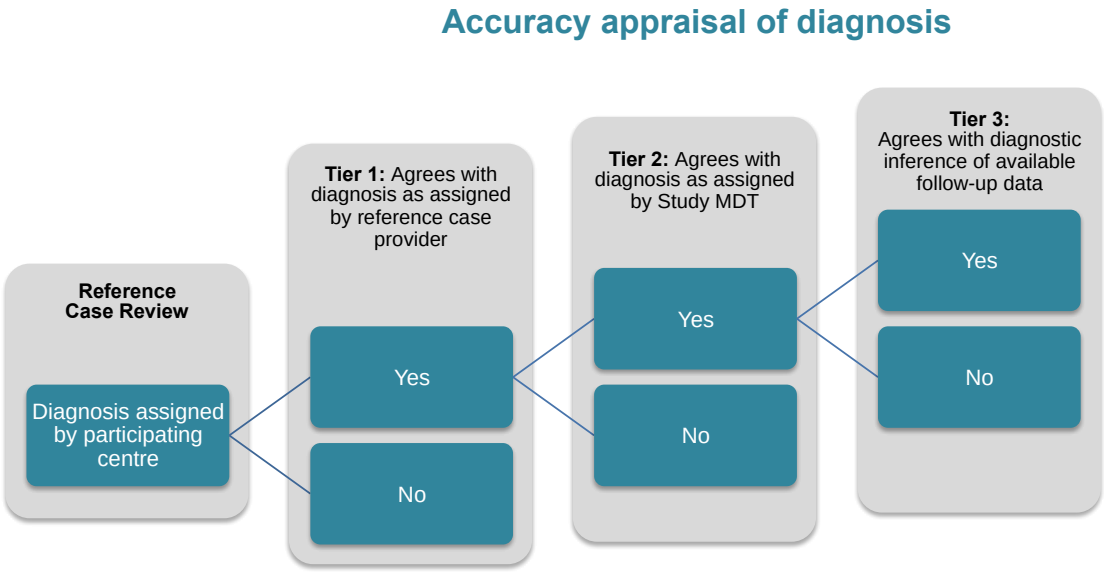
Tier 2 "gold standard" (for application only when further evaluating the accuracy of cases fulfilling the Tier 1 definition): a second definition of accurate diagnosis will be used for which an accurate diagnosis will be one ***"in agreement with a diagnosis assigned by the Study MDT"***. In this instance, the study MDT will be a quasi MDT comprising an expert clinician; radiologist and pathologist from the study co-Principal Investigators.

This definition will provide a source of external (expert) validation of the Tier 1 diagnosis of accuracy, but will be limited in its absolute accuracy by the artificial nature of the MDT meaning that its members: (i) do not work together routinely as a team, and (ii) will have had no direct contact with the patient to inform their decision making.

Tier 3 "gold standard" (for application only when further evaluating the accuracy of cases fulfilling the Tier 2 definition): a third definition of level of diagnostic accuracy will be applied, for which an accurate diagnosis will be one ***"in agreement with the diagnosis in line with confirmatory/supporting follow-up data".***

[3] i.e. to achieve this end, it will not be possible to request reference case centres provide (for example) their most recent 20 cases

This definition will provide independent validation of the Tier 1 & 2 diagnosis, enabling accuracy of diagnosis to be inferred from resultant morbidity and mortality records.



6.3. METHODOLOGY

Phase II participants will be selected / invited from the group of Phase I MDT questionnaire respondents/sites, subject to appropriate consideration of the design issues outlined in section 6.2.

Reference cases (n=50-80[4]) will be invited from selected members of the study steering committee with possible inclusion of some typical case examples sourced from centres participating in Phase I.

The cases will be digitised (including pathology data) and distributed to participating centres via a secure (password protected) web-based hosting system.[5]

The online system will enable overall and per site / participant monitoring, including:

- **Overall case review status**: across all participating sites and, at site level, completed / partially complete / not started
- **Completion time:** average time associated with overall and single case review.

The system will enable centralization of participant diagnostic responses as well as operational queries and administrator responses. It will also offer manual and automatic reminder functionality to support administrator follow up across sites and hep maximise case review completion.

[4] Final number will be informed by Phase I characterization of real-world case mix to ensure the reference case selection is sufficient to power an analysis of IPF diagnosis within the overall case mix while minimising inherent selection bias

[5] If the methodology development of Phase I (and phase I findings) suggest that digital information delivery is not feasible or appropriate in some participating countries/regions a decision will be taken by the study steering group and supporting stakeholders as to whether it is necessary and viable to run a hard copy process in parallel.

6.4 OUTCOMES

The Phase II global e-evaluation of ILD diagnostic accuracy and accuracy will result in a:

- **Descriptive analysis of participating MDTs:**
  - Organisation & structure of MDT; Governance of MDT; Information generated by MDT
- **Descriptive analysis of MDT accuracy, against:**
  - Tier 1 definition of diagnostic accuracy; Tier 2 definition of diagnostic accuracy; Tier 3 definition of diagnostic accuracy
- **Concordance / measure of agreement across centres (e.g. kappa statistics):**
  - Total; Within-country; Within-continent/region; Stratified by MDT composition; Stratified by ILD condition (IPF, non-IPF)
- **Analysis of independent MDT features associated with diagnostic accuracy** (e.g. predictors of MDT diagnostic accuracy).
- **Recommendations associated with optimising the diagnostic process**, informed by current practice approaches associated with best outcomes (agreement across Tier 1-3 accuracy definitions) and also by practical considerations of resource availability and current practices, as ascertained in Phase I.

The Phase II study outputs will provide valuable evidence to inform guideline recommendations as well as best practice recommendations.

7. REGISTRATION

The study will be registered in the European Network of Pharmacoepidemiology and Pharmacovigilance (ENCePP) global e-registry of studies.

8. REPORTING AND PUBLICATION OF RESULTS

As with all studies supported or sponsored by the Respiratory Effectiveness Group (REG; www.effectivenessevaluation.org), the study findings will be published in appropriate peer-reviewed scientific journals. A manuscript from each phase of the study will be submitted to a relevant journal within 12 months of completion of the respective study phase.

Dissemination pathways may also include conference abstracts and presentations, as appropriate.

9. COLLABORATION

9.1 INDEPENDENT STEERING COMMITTEE

The study will be overseen and implemented by an independent, international steering committee working collaboratively through the REG ILD Working Group. The steering committee will include REG ILD Working Group Members and National Leads (see Table 1).

The committee will work across both phases (I and II) of the study, providing continuity, clinical expertise (e.g. reviewing and advising on study methodology,

accuracy and interpretation of results) and geographical and operational guidance (e.g. translation/language and healthcare system insights and engagement and coordination of appropriate collaborators and a collaborating centres).

The committee will also oversee and co-author the final study manuscript(s).

Table 3. REG ILD Working Group Steering Committee Members

Collaborator	Country	Affiliation
Luca Richeldi	UK	University of Southampton, UK
Simon Walsh	UK	Kings College Hospital, London
Fernando J. Martinez	USA	Weill Cornell Medical College, New York
Kevin Flaherty	USA	University of Michigan, Ann Arbor, MI
Jeffrey Myers	USA	University of Michigan, Ann Arbor, MI
Ganesh Raghu	USA	University of Washington, Washington
Kevin Brown	USA	National Jewish Health, Denver, CO
Harold Collard & Kaissa DeBoer	USA	University of California, San Francisco, CA
Martin Kolb	Canada	McMaster University, Hamilton, ON
Christopher Ryerson	Canada	University of British Columbia, Vancouver, BC
Francesco Bonella	Germany	University of Duisburg-Essen, Essen
Jürgen Behr	Germany	University of Munich, Munich
Vincent Cottin	France	Lyon University Hospitals, Lyon
Bruno Crestani	France	Hopital Bichat Paris, France
Toby Maher	UK	National Heart and Lung Institute, Imperial College, London
Athol U. Wells	UK	Royal Brompton Hospital, London
Ian Glaspole	Australia	Alfred Health, Melbourne
Tamera Corte	Australia	University of Sydney, Sydney
Manuela Funke & Thomas Geiser	Switzerland	University Hospital Bern, Bern
Paolo Spagnolo	Italy	University of Padua, Padua, Italy
Paola Rottoli	Italy	Le Scotte Hospital, Siena
Carlo Vancheri	Italy	University of Catania, Catania
Maria Molina Molina, Pilar Rivera; Lurdes Planas	Spain	Hospital Universitario de Bellvitge, Barcelona, Spain
Claudia Valenzuela	Spain	Hospital Universitario de La Princesa Madrid
Demosthenes Bouros	Greece	University of Athens, Athens
Katerina M. Antoniou	Greece	Department of Thoracic Medicine, Medical School, University of Crete
Giovanni Ferrara & Magnus Sköld	Sweden	Karolinska University Hospital, Solna, Sweden
Aileen David Wang & Camillo Roa	Philippines	University of the Philippines-Philippine General Hospital, Manila, Philippines
Antonio Morais	Portugal	Centro Hospitalar de São João, Porto, Portuga
Arata Azuma	Japan	Nippon Medical School, Tokyo
Mariano Mazzei	Argentina	University of Buenos Aires, Buenos Aires
Silvia Quadrelli	Argentina	Hospital Británico de Buenos Aires, Argentina
Moises Selman	Mexico	Instituto Nacional de Enfermedades Respiratorias

9.2 INDUSTRY COLLABORATION

Gaining new insights into the complex diagnostic processes and pathways that exist in everyday routine care is of benefit to a wide range of stakeholders (both clinical and commercial) with the shared end goal of optimizing appropriate use of therapies for the benefit of the patient.

Multi-stakeholder engagement and will be sought to ensure a collaborative approach, one that draws on a wide range of knowledge and network of contacts, is taken. Potential collaborating organisations are summarised in Table 4.

Table 4. Potential Study Supporters and Collaboration Organisations

Collaborating Supporter	Based in	Company
Mike Rosenbluth; Pauline Bianchi	USA	Veracyte
Armin Furtwaengler; Craig Conoscentti	Germany	Boheringer Ingelheim
Rakesh Kantaria	USA	AstraZeneca
Diana Gallagher; Shelia Violette	USA	Biogen Idec
Ben Kramer; Jonathan Sorof; Klaus-Uwe Kirchgässler	USA, Germany	Genentech Roche
Richard Marshall; Billy Fahey	UK	GSK
Jeffery Wager	USA	Proterris
Tom O'Riordan	USA	Gilead
Christine Soubrane	France	Sanofi-Aventis
Beth Trehu	Japan	Promedior
Brigit Haier	USA	UBC
Claudio Pasquninelli	USA	BMS
Seth Porter	USA	FibroGen

10. TIME SCHEDULE AND DELIVERY

The anticipated length of Phase I of the study will be approximately 24 months (from contract signature to publication and initiation of Phase II). An indicative timeline is summarised below. More accurate timelines will be generated once funding and collaborative partners have been identified and confirmed.

Table 2. Anticipated study timelines

	Study Component		Indicative Timeline
Set up	Contracts & Funding	Signing of all contracts & necessary agreements with supporting organisations and study sponsor	Q4 2015
		Signing of all contracts & necessary agreements with national vendors (as required)	Q1 2016
Phase I	Review / Adaption of Methodology	Steering Committee review & adaption of screening methodology	Q1 2016
		National/regional validation and/or adaptation (including translation) of screening methodology	Q2 2016

	Systematic Data Collection	Commence	Q3 2016
		Conclude	Q4 2016
	Analysis	Data Cleaning & master file generation	Q1 2017
		Analysis: full population and stratified by region	Q1 2017
	Publication	Draft Development	Q2 2017
		Final manuscript submitted	Q2/3 2017
Phase II	Planning & design	Protocol development for Phase II analysis*	Q1-Q2 2017
		Commencement of Phase II	Q3 2017
	Preparation	Securing, digitisation reference cases	Q3 2017
		Distributing reference cases	Q4 2017
	Systematic Data Collection	Commence	Q4 2017
		Conclude	Q2 2018
	Analysis	Data Cleaning & master file generation	Q3 2018
		Analysis: full population and stratified by region	Q4 2018
		Interpretation & recommendation development	Q1 2019
	Dissemination	Manuscript Development: 1 x results; 1 x recommendations	Q4 2018 Q1/2 2019
		Manuscript Submission: 1 x results; 1 x recommendations	Q1 2019 Q2/3 2019

*informed by Phase I

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