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General Information

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Are external grants or funds being used to support this research?: External grants or funds are being used to support this research.
Project Funding Source: PI is funded by NIHR grant
How did you learn about the YODA Project?: Other

Conflict of Interest

https://yoda.yale.edu/system/files/scan_2020_physreviewisi1.pdf
https://yoda.yale.edu/system/files/yoda_project_coi_form_fk.pdf
https://yoda.yale.edu/system/files/gauri_coi_physiology.pdf
https://yoda.yale.edu/system/files/kr_physiology.pdf
https://yoda.yale.edu/system/files/gisli_physiology2.pdf

Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.
Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

1. NCT00391443 - AC-052-321 - Effects of Bosentan on Morbidity and Mortality in Patients With Idiopathic Pulmonary Fibrosis - a Multicenter, Double-blind, Randomized, Placebo-controlled, Parallel Group, Event-driven, Group Sequential, Phase III Study
2. NCT00071461 - AC-052-320 (BUILD 1) - A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Assess the Efficacy, Safety, and Tolerability of Bosentan in Patients With Idiopathic Pulmonary Fibrosis, Open Label Extension
3. NCT00903331 - AC-055B201 - A Double-blind, Randomized, Placebo-controlled, Multicenter, Parallel Group Study to Evaluate the Efficacy, Safety, and Tolerability of Macitentan in Patients With Idiopathic Pulmonary Fibrosis

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

A systematic review and individual patient data meta-analysis of physiological biomarkers in idiopathic pulmonary fibrosis

Narrative Summary:

Idiopathic pulmonary fibrosis (IPF) is a devastating condition which causes scarring of the lungs and affects around 3 million people worldwide. Disease trajectory is variable, with some patients progressing much quicker than others. Identifying early predictors of progression may enable relevant therapies to be offered at an early stage. Physiological biomarkers such as lung function (FVC, DLCO) and total distance walked in 6 minutes (6MWD) are non-invasive measurements. We therefore hope to collate data from clinical trial placebo arms to explore whether short term change in these measurements may be able to predict clinical outcomes. This will help better inform healthcare professionals.

Scientific Abstract:

Prospero protocol: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=164935

Background: Idiopathic Pulmonary Fibrosis (IPF) is a devastating lung condition of unknown origin, characterised by variable and unpredictable disease behaviour. A number of studies evaluating the role of physiological biomarkers in predicting progression have been published.

Objectives: We aim to conduct a systematic review and meta-analysis of individual patient data of treatment naive IPF patients (placebo arm) to assess whether baseline and/or short term change in physiological biomarkers can

accurately predict important clinical outcomes such as disease progression and mortality.

Study Design: Individual patient data from randomised interventional clinical trial placebo arms will be analysed, and a two-step meta-analysis performed.

Participants: Adult patients with untreated IPF evaluated in interventional clinical trials (placebo arms only).

Main outcome measures: Mortality and disease progression (defined as relative decline in forced vital capacity of at least 10%, or death, at 12 months)

Statistical analysis: Individual patient data will be sought and a two-step meta-analysis performed adjusted for a priori confounders including age, sex and smoking status. Hazard ratios for baseline and three month change of physiological parameters in predicting mortality will be calculated. Disease progression will be standardised as 10% relative decline in FVC or death within 12 months of baseline, and odds ratios for predicting disease progression calculated.

Brief Project Background and Statement of Project Significance:

Idiopathic pulmonary fibrosis (IPF) is a devastating lung condition of unknown origin characterised by progressive and irreversible interstitial fibrosis. Although median survival is 3 years, IPF is manifest by variable and unpredictable disease trajectory amongst individual patients. Advances in the management of IPF are hampered by the absence of validated prognostic measures, especially biomarkers that change over short time periods. Physiological biomarkers (such as but not limited to forced vital capacity (FVC), diffusing capacity for carbon monoxide (DLCO) and six minute walk distance (6MWD)) may be suitable as early predictive markers of disease behaviour enabling stratification of therapy and personalised medicine.

We aim to conduct a systematic review and meta-analysis of individual patient data of treatment naive IPF patients (placebo arm) to assess whether baseline and/or short term change in physiological biomarkers can accurately predict important clinical outcomes such as disease progression and mortality.

Specific Aims of the Project:

Research question - Do baseline values or 3-month change in physiological (FVC, DLCO, 6MWD) biomarkers predict disease progression and mortality in untreated patients with idiopathic pulmonary fibrosis?

What is the purpose of the analysis being proposed? Please select all that apply.
Participant-level data meta-analysis
Participant-level data meta-analysis pooling data from YODA Project with other additional data sources

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:

Types of study to be included
Inclusion: Placebo arms of randomised interventional clinical trials in adult (aged>18) patients with IPF.

Exclusion: Non-interventional studies, conference abstracts, letters, commentaries, correspondence, case reports, expert opinions, editorials, other non-original systematic reviews, retrospective studies and animal studies. Studies investigating non-IPF Interstitial Lung Diseases. Studies with sample size n<30 will be excluded to minimise heterogeneity and bias.

Other studies to be included:

PMID: 14711911 CSDR
PMID: 15665326 Author contacted
PMID: 16306520 Zambon
PMID: 17901413 Yoda
PMID: 18669816 CSDR

PMID: 19570573 CSDR
PMID: 19996196 Author contacted
PMID: 20007927 Author contacted
PMID: 21474646 Yoda
PMID: 21571362 CSDR
PMID: 21992121 Vivli
PMID: 22257422 Author contacted
PMID: 22561965 Vivli
PMID: 23648946 Gilead
PMID: 23682110 Yoda
PMID: 23143842 Author contacted
PMID: 24836309 Vivli
PMID: 24836312 CSDR
PMID: 24836310 Vivli
PMID: 24836310 Vivli
PMID: 30201408 Bristol-Myers Squibb
PMID: 28787186 MedImmune contacted directly
PMID: 31575509 FibroGen contacted directly
PMID: 21362103 CSDR

Main Outcome Measure and how it will be categorized/defined for your study:

Participants/population
Adult patients aged > 18 with untreated idiopathic pulmonary fibrosis diagnosed according to contemporaneous consensus guidelines.
Intervention(s), exposure(s)
Physiological biomarkers (Forced Vital Capacity, Gas transfer and 6-minute walk test) at the following time points:
1) Baseline
2) Change over 3 months.
Comparator(s)/control
Age, Gender, Smoking
Context
Main outcome(s)
Overall mortality.
Timing and effect measures
All time periods.
Additional outcome(s)
1) Absolute or relative percentage change from baseline in FVC at 12 months
2) Disease progression at 12 months defined as:
a. >10% relative decline in FVC
b. Death
Timing and effect measures
12 months.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:

Baseline FVC, DLCO and 6 min walk distance
Change in 3 month of above parameters

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:

- Patient pseudoID
- Age at consent
- Height (cm)
- Ethnicity
- Gender (M or F)
- Smoking (ever or never)
- Follow up time (days)

- Dead or alive at end
- Time to death (days)
- Baseline FVC (L)
- Baseline FVC (% predicted)
- 3 month FVC (L)
- 3 month FVC (% predicted)
- 12 month FVC (L)
- 12 month FVC (% predicted)
- Baseline DLCO (% predicted)
- Baseline DLCO (ml/min/mmHg)

Statistical Analysis Plan:

A narrative synthesis of the findings from the included studies will be presented according to the review question, with summary tables inclusive of study and participant characteristics. Derivation and validation cohorts from the same study will be treated as two individual cohorts.

Correlation of physiological performance over 3 months and twelve months from baseline will be assessed in a repeated measures design, relevant time-point meta-analysis. Individual patient data will be sought and a two-step meta-analysis performed adjusted for a priori confounders including age, sex and smoking status.

Hazard ratios for baseline and three month change of physiological parameters in predicting mortality will be calculated. Disease progression will be standardised as 10% relative decline in FVC or death within 12 months of baseline, and odds ratios for predicting disease progression calculated. Data will be graphically displayed using forest plots.

Heterogeneity will be assessed by Cochran's Q and I^2 using random effects. Synthesis criteria exclude sample sizes that are not conducive to random effect models ($n<30$). Where heterogeneity is high, sensitivity analyses will be performed using inverse variance heterogeneity models.

Data from individual platforms will be combined using a two-step approach. In the first step, data will be analysed using the YODA secure research environment and summary estimates calculated. Summary estimates/coefficients will thereafter be downloaded and imported into STATA alongside summary estimates from other studies/platforms, and a meta-analysis performed, taking into account individual study weighting.
Software Used:
STATA
Project Timeline:

Start date - 1st Feb 2020
Analysis completion date - 1st Dec 2020
Manuscript drafted/results reported back to Yoda - 1st Feb 2021

Dissemination Plan:

All data will be anonymised and grouped for presentation and publication. The results from this study will be publicised at regional and national conferences as well as being submitted for publication in open access peer-reviewed journals in accordance with UK Research Council policies. No participants will be identified in any publications that arise from this research.
Conferences work to be submitted to include: British Thoracic Society Winter Meeting, European Respiratory Society Congress
Journals - Thorax

Bibliography:

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10.1056/NEJMra1705751 [published Online First: 2018/05/10]
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Supplementary Material:

https://yoda.yale.edu/sites/default/files/prospero_pdf.pdf