

Principal Investigator

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General Information

Key Personnel (in addition to PI):

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Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.

How did you learn about the YODA Project?: Data Holder (Company)

Conflict of Interest

https://yoda.yale.edu/system/files/sv_6m4tghhxg7w7uxe-r_2zk1kq0fkrjeq0s.pdf
https://yoda.yale.edu/system/files/yoda_coi_is.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. [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

An individual patient data meta-analysis of clinical endpoints in pulmonary hypertension with interstitial lung disease (ILD-PH)

Narrative Summary:

To inform trial designs that recruit people with pulmonary hypertension and interstitial lung disease, what effect sizes do pharmaceutical interventions lead to on clinical and functional outcomes when compared to placebo? Pulmonary hypertension (PH) is a common complication of interstitial lung disease (ILD) and is associated with further exercise limitation and poor prognosis. PH in association with ILD (PH-ILD) is often treated with pulmonary vasodilators although few data exist to support this practice. In order to design effective clinical trials it is essential that randomised control trials (RCT) are powered on appropriate end points.

Scientific Abstract:

Background

An individual patient data meta-analysis of clinical endpoints in pulmonary hypertension with interstitial lung disease (ILD-PH) to determine appropriate clinical endpoints for future randomised clinical control trials.

Objective

To inform trial designs that recruit people with pulmonary hypertension and interstitial lung disease, what effect sizes do pharmaceutical interventions lead to on clinical and functional outcomes when compared to placebo.

Pulmonary hypertension (PH) is a common complication of interstitial lung disease (ILD) and is associated with further exercise limitation and poor prognosis. PH in association with ILD (PH-ILD) is often treated with pulmonary vasodilators although few data exist to support this practice. Indeed, a number of studies of patients with mainly mild PH have been negative. In order to design effective clinical trials to test pharmacological interventions in those with PH-ILD, it is essential that randomised control trials (RCT) are powered on appropriate endpoints with feasible recruitment strategies.

Study Design

Randomized Controlled Trials with results published in peer-reviewed literature or as conference proceedings will be included. Quasi-randomised and cross-over trials are eligible but unit-of-analysis will be standardised to avoid errors and violation of analytical assumptions. All non-randomised study designs and case studies will be excluded.

Participants

Anonymised individual participant data

Primary Outcomes and Secondary Outcomes

Primary outcomes:

Mortality

Secondary outcomes:

Change in mean pulmonary arterial pressure (mPAP)

Change in pulmonary vascular resistance (PVR)

Change in six minute walk distance (6MWD)

Change in health related quality of life scores

Statistical Analysis

Analyses will be restricted to people with evidence of PH and ILD, regardless of PH or ILD severity.

A random-effects inverse-variance meta-analysis will be used, heterogeneity in effect will be assessed by I² and the DerSimonian-Laird estimate of tau². GRADE certainty of evidence guidelines will be used to assess the review findings.

The IPD meta-analysis will take a two-step method, estimating study level effects independently using patient-level data with Cox and generalised linear models, which will be subsequently included in a meta-analysis of the aggregated outcomes at study-level. Individual participant data will enable consistent adjustments in multivariable models (e.g. age, sex, BMI), as well as restriction of PH trial data to ILD specific diagnoses, and the opportunity to assess consistent follow-up times.

Brief Project Background and Statement of Project Significance:

To inform trial designs that recruit people with pulmonary hypertension and interstitial lung disease, what effect sizes do pharmaceutical interventions lead to on clinical and functional outcomes when compared to placebo?

Pulmonary hypertension (PH) is a common complication of interstitial lung disease (ILD) and is associated with further exercise limitation and poor prognosis. PH in association with ILD (PH-ILD) is often treated with pulmonary vasodilators although few data exist to support this practice. Indeed, a number of studies of patients with mainly mild PH have been negative. In order to design effective clinical trials to test pharmacological interventions in those with PH-ILD, it is essential that randomised control trials (RCT) are powered on appropriate endpoints with feasible recruitment strategies.

Specific Aims of the Project:

Aim

To synthesis evidence from randomised control trial designs using a specific focus on people with PH-ILD, providing an evidence base for the most appropriate endpoint to power studies within this patient group.

Primary hypothesis:

Restriction of PH trial cohorts using ILD criteria will identify a beneficial effect of vasodilator drug intervention on mortality

Secondary hypothesis:

Restriction of PH trial cohorts using ILD criteria will identify valuable clinical endpoints to power prospective clinical trials

What is your Study Design?:

Meta-analysis (analysis of multiple trials together)

What is the purpose of the analysis being proposed? Please select all that apply.

New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations

Participant-level data meta-analysis

Meta-analysis using data from the YODA Project and other data sources

Research Methods

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

Participants must have a diagnosis of Pulmonary Hypertension(PH).

Pre-Capillary PH
mPAP > 20 mmHg
PAWP ?15 mmHg
PVR > 2 WU

IpcPH
mPAP > 20 mmHg
PAWP > 15 mmHg
PVR ?2 WU

CpcPH
mPAP > 20 mmHg
PAWP > 15 mmHg
PVR > 2 WU

CpcPH, combined post- and pre-capillary pulmonary hypertension; IpcPH, isolated post-capillary pulmonary hypertension; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; WU, Wood units.

Some patients present with elevated mPAP (>20 mmHg) but low PVR (?2 WU) and low PAWP (?15 mmHg); this haemodynamic condition may be described by the term 'unclassified PH'

Primary and Secondary Outcome Measure(s) and how they will be categorized/defined for your study:

Primary outcomes:
Mortality

Secondary outcomes:
Change in mean pulmonary arterial pressure (mPAP)
Change in pulmonary vascular resistance (PVR)
Change in six minute walk distance (6MWD)
Change in health related quality of life scores

Additional outcome(s)
Change in percent predicted forced vital capacity (FVC)
Change in percent predicted DLco
Change in forced expiratory volume 1 (FEV1)/FVC ratio
Change in percent predicted Kco (carbon monoxide transfer coefficient)
Change in exercise or endurance
Change in desaturation or oxygen requirements
Change in B-type natriuretic peptide (BNP) or N-terminal proBNP (NT-proBNP)
Change in participant reported health related quality of life
PH-ILD related hospital admissions
Adverse events
Relevant composites of the above

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

Measures of effect
Continuous endpoints will be assessed using standardised mean difference between placebo and intervention. Risk ratios will be used for dichotomised endpoints. Cox proportional hazard models will be used for time to event estimates. To enable power calculations for future interventional trials, standardised effect sizes (Hedge's g) will be estimated between placebo and treatment arms.

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

Demographics (age, gender, ethnicity, height, weight, diagnosis); baseline (PH severity, lung function, endurance,

quality of life, oxygen requirements, B-type natriuretic peptide levels [BNP]), follow-up (timing, severity, lung function, endurance, quality of life, oxygen requirements, BNP levels, survival, serious adverse events, hospital admissions)

Statistical Analysis Plan:

Studies identified through a systematic search strategy will be screened independently by two authors. Individual patient data (IPD) will be sought from trial authors/data repositories using a bespoke data collection proforma. A two-step IPD meta-analysis will be performed and restricted to participants with evidence of an interstitial lung disease diagnosis obtained from patient-level data of clinical trials assessing effects of vasodilator intervention on pulmonary hypertension outcomes.

Analyses will be restricted to people with evidence of PH and ILD, regardless of PH or ILD severity. The primary analysis will test the outcome of mortality according to study arm: vasodilator intervention compared to placebo/standard of care. Secondary analysis will test study intervention on additional outcomes reported within a minimum of three available studies, including change in 6 minute walk test, time to clinically defined progression, change in patient reported quality of life, change in forced vital capacity, change in pulmonary arterial pressure, change in vascular resistance.

A random-effects inverse-variance meta-analysis will be used, heterogeneity in effect will be assessed by I² and the DerSimonian-Laird estimate of tau². GRADE certainty of evidence guidelines will be used to assess the review findings.

The IPD meta-analysis will take a two-step method, estimating study level effects independently using patient-level data with Cox and generalised linear models, which will be subsequently included in a meta-analysis of the aggregated outcomes at study-level. Individual participant data will enable consistent adjustments in multivariable models (e.g. age, sex, BMI), as well as restriction of PH trial data to ILD specific diagnoses, and the opportunity to assess consistent follow-up times (Burke et al. 2017). We have previously used the two-stage approach in analysis of FVC from clinical studies across different research environments (Khan et al. 2022).

Secure research environments will be accessed to determine study level effects (step-1). Where patient-level data is available in an alternative research environment, study level estimates will be incorporated into the step-2 meta-analysis using the same step-1 model. In step-2, study effects are included with standard errors in a meta-analysis, maintaining the independence of each individual study as these becomes the unit of observation. IPD will never be extracted from research environments.

The Vivli research environment has potential access to the required clinical trial datasets that were identified as important in addressing the hypothesis through a systematic search strategy, therefore Vivli will be used to perform both step-1 and step-2 methods. This will contribute substantially to inverse-variance model of meta-analysis. Study-level estimates obtained in alternative environments will be added at step-2 within the Vivli environment.

Data extraction (selection and coding)

Studies for analysis will be screened by two authors independently. Conflicts will be resolved by involvement of a senior author.

Risk of bias (quality) assessment

The risk of bias assessment will be conducted by two authors independently, using the Revised Tool for Risk of Bias in Randomised Trials (RoB-2.0).

A narrative synthesis of the risk of bias findings from the included studies will be presented with summary tables for study characteristics.

I² heterogeneity will be classified as follows:

1. 0% to 40%: might not be important;
2. 30% to 60%: may represent moderate heterogeneity;
3. 50% to 90%: may represent substantial heterogeneity;
4. 75% to 100%: may represent considerable heterogeneity.

Missing Values

Analyses will be performed using listwise deletion to exclude participants that have missing exposure, covariate or

outcome data in the individual level data within each study

Software Used:

STATA

Project Timeline:

Approximately 6 months

Dissemination Plan:

Publication in a high impact journal, we will be aiming for Thorax or the American Journal of Respiratory and Critical Care Medicine.

Bibliography:

David G. Kiely, Robin Condliffe (2021) Assessing pulmonary hypertension severity in lung disease is a key step to improving outcomes: embrace resistance and don't be pressurised to go with the flow. *European Respiratory Journal* 58.

Burke D, Ensor J, Riley R (2017). Meta-analysis using individual participant data: one-stage and two-stage approaches, and why they may differ. *Statistics in Medicine* 36.

Khan FA, Stewart I, Moss S, Fabbri L, Robinson KA, Johnson SR, Jenkins RG (2022). Three-Month FVC Change: A Trial Endpoint for Idiopathic Pulmonary Fibrosis Based on Individual Participant Data Meta-analysis. *Am J Respir Crit Care Med*. PMID: 35020580.

Supplementary Material:

https://yoda.yale.edu/sites/default/files/crd42022307551_0.pdf

<https://yoda.yale.edu/sites/default/files/trialsfordatarequest.docx>

<https://yoda.yale.edu/sites/default/files/31032023.docx>