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To cite this version:

Francois Alexandre, Virginie Molinier, Maurice Hayot, Guillaume Chevance, Gregory Moullec, et al.. Association between long-term oxygen therapy provided outside the guidelines and mortality in patients with COPD. BMJ Open, 2022, 12 (1), pp.e049115. 10.1136/bmjopen-2021-049115 . hal-03523124

HAL Id: hal-03523124

https://hal.science/hal-03523124v1

Submitted on 12 Jan 2022

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Association between long-term oxygen therapy provided outside the guidelines and mortality in patients with COPD

Francois Alexandre ,[1] Virginie Molinier,[1] Maurice Hayot,[2] Guillaume Chevance,[3] Gregory Moullec,[4] A n Varray ,[5] Nelly Héraud[1]

ABSTRACT

Introduction Hypoxaemia is a frequent complication of chronic obstructive pulmonary disease (COPD). To prevent its consequences, supplemental oxygen therapy is recommended by international respiratory societies. However, despite clear recommendations, some patients receive long-term oxygen therapy (LTOT), while they do not meet prescription criteria. While evidence suggests that acute oxygen supply at high oxygenation targets increases COPD mortality, its chronic effects on COPD mortality remain unclear. Thus, the study will aim to evaluate through a systematic review and individual patient data meta-analysis (IPD-MA), the association of LTOT prescription outside the guidelines on survival over time in COPD.

Methods Systematic review and IPD-MA will be conducted according to Preferred Reporting Items for a Systematic Review and Meta-Analyses IPD guidelines. Electronic databases (PubMed, Web of Science, EMBASE, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, OpenGrey and BioRxiv/MedRxix) will be scanned to identify relevant studies (cohort of stable COPD with arterial oxygen tension data available, with indication of LTOT filled out at the moment of the study and with a survival follow-up). The anticipated search dates are January–February 2022. The main outcome will be the association between LTOT and time to all-cause mortality according to hypoxaemia severity, after controlling for potential covariates and all available clinical characteristics. Quantitative data at the level of the individual patient will be used in a one-step approach to develop and validate a prognostic model with a Cox regression analysis. The one-step IPD-MA will be conducted to study the association and the moderators of association between supplemental oxygen therapy and mortality. Multilevel survival analyses using Cox-mixed effects models will be performed.

Ethics and dissemination As a protocol for a systematic review, a formal ethics committee review is not required. Only studies with institutional approval from an ethics committee and anonymised IPD will be included. Results will be disseminated through peer-reviewed publications and presentations in conferences.

PROSPERO registration number CRD42020209823.

- Systematic review will provide the most important dataset available on patients with long-term oxygen therapy (LTOT) prescription outside current guidelines
- The individual patient data (IPD) meta-analysis will offer new evidences concerning the association between LTOT provided outside the guidelines and mortality hazard rates.
- The observational data collected in this study will be closer to real-world data than in previous randomized controlled trials.
- Limitation includes the impossibility to directly conclude on the existence of a potential cause–effect relationship between LTOT and mortality.
- Limitation also lies on the ability to acquire the IPD and on the evaluation of the heterogeneity of the study designs and studied populations.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common respiratory illness involving near to 9% of adult population and becoming the third cause of death in the world.[1 2] This disease leads, among others, to respiratory problems, pulmonary hypertension, heart failure, neurocognitive and neuromuscular dysfunctions and systemic inflammation.[3] Directly linked to the respiratory complications, patients with COPD usually suffer from hypoxaemia issues (transient when limited to sleep or exercise or chronic when also occurring at rest). The degree of hypoxaemia worsens with the progression of the disease up to respiratory insufficiency. Hypoxaemia is classically defined as an abnormally arterial oxygen tension level (PaO_2) lower than 80 mm Hg or an arterial oxygen saturation (SaO_2 or SpO_2) lower than 93% at rest while breathing ambient air.[4 5] In COPD, severe hypoxaemia is defined as PaO_2 breathing room air at rest less than 55 mm Hg or less than 59 mm Hg with concurrent polycythaemia or signs of right-sided heart failure or pulmonary hypertension. Therefore, non-severe hypoxaemia (ie, mild to moderate) is seen as a PaO_2 higher than 59 mm Hg but less than normal value (80 mm Hg in general or less according to age[6 7]).

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Hypoxaemia is considered as a major complication of COPD, notably associated with decreased exercise tolerance[8] and increased mortality.[9] To prevent its consequences, supplemental oxygen therapy is usually prescribed either in case of transient hypoxaemia during exercise or/and sleep, or in case of chronic hypoxaemia using a long-term oxygen therapy (LTOT) device (ie, prescription of supplemental oxygen therapy at least 15 hours per day). LTOT has been recommended for decades by international guidelines for severe hypoxaemic patients exclusively.[10 11] These recommendations are based on two landmark studies published in early 1980s, which are the sole to date to have demonstrated some substantial benefits of providing LTOT in COPD. Briefly, the Medical Research Council study reported higher survival rate of 5 years after randomisation in severe hypoxaemic patients receiving supplemental oxygen therapy for greater than 15 hours per day versus no oxygen at all.[12] In addition, the Nocturnal Oxygen Therapy Trial study found higher survival rate of 3 years after randomisation in severe hypoxaemic patients receiving continuous supplemental oxygen therapy versus those receiving 12 hours nocturnal supplemental oxygen therapy.[13]

Although the last international guidelines recommend to restrain LTOT to severe hypoxaemic patients,[14 15] several studies reported a large proportion of patients under LTOT (around 40%) while having only mild-to-moderate hypoxaemia.[16–20] These prescriptions of LTOT outside current guidelines (ie, supplemental oxygen therapy prescribed at least 15 hours per day in patients with no severe hypoxaemia) can be explained by at least two reasons. First, LTOT is most of the time prescribed after an exacerbation, thus in an instability context, and without further reevaluation of the patient's need.[21 22] However, hypoxaemia status is variable and some patients may recover over time. For instance, it has been shown that up to 40% patients who meet criteria for LTOT prescription at a given time have spontaneously recovered 1–3 months later.[18] Second, LTOT is sometimes prescribed outside the guidelines for prevention or convenience purposes. Indeed, almost 20% of patients are prescribed LTOT while not having severe hypoxaemia even at the time of prescription.[23 24] This lack of adherence to LTOT prescription guidelines could be linked to the embedded culture of 'more is better' and 'it's just oxygen, it doesn't do any harm', which has been highlighted in a recent qualitative survey on the myths and beliefs regarding oxygen therapy prescription.[19]

In addition to the considerable economic costs generated, the health consequences of LTOT provided outside the guidelines are an important issue by unnecessarily exposing patients to the potential adverse effects of hyperoxia. These effects have already been documented under acute exposition. Indeed, a randomized controlled trial (RCT) on patients with acute exacerbated COPD found that high flow oxygen therapy (hyperoxaemia) in the pre-hospital setting, compared with titrated supplemental oxygen therapy (normoxaemia) induced an almost five-time increase of mortality.[25] Furthermore, an additional retrospective study on patients with exacerbated COPD admitted in intensive care unit found that hyperoxaemia, that had occurred in 24% of patients, was associated with an increased risk of serious inpatient adverse outcomes (death, assisted ventilation or respiratory failure) (OR=9.17, 95% CI 4.08 to 20.60).[26] Altogether, these data show that supplemental oxygen therapy at high oxygenation targets increases COPD mortality in the acute settings.

However, while the potential adverse effects of acute oxygen supply in COPD have been established, those induced by chronic exposition are inconsistent. The impact of LTOT in mild-to-moderate hypoxaemic patients with COPD has been assessed in two RCTs, both showing no effect on mortality risk.[27 28] However, they both have important limitations that impede any definitive conclusion. First, the study of Górecka *et al*[27] recorded too small numbers of deaths to conclude with certainty on the absence of mortality rate differences between groups (only 38 and 32 non-survivors in the LTOT and control group, respectively). Furthermore, the Long-term Oxygen Treatment Trial (LOTT)[28] only indirectly estimated hypoxaemia severity through pulsed oxygen saturation (SpO_2). While the authors targeted to enrol patients with an SaO_2 between 89% and 93%,[28] which is thought to be equivalent to a PaO_2 of 59–70 mm Hg, SpO_2 is known to give a mean SaO_2 overestimation of 4 points.[29] Thus, with a mean SpO_2 of 92%, it is possible that some patients had severe hypoxaemia instead of mild-to-moderate one in the LOTT study.[28] Besides those RCTs, a few retrospective observational studies also aimed to assess the association between mortality and LTOT prescription outside the guidelines.[17 20 30] On one hand, Drummond *et al*[17] found an association between mortality and LTOT outside the guidelines, but it was not significant anymore after controlling by confounding factors. On the other hand, Alexandre *et al*[30] and Pavlov *et al*[20] reported a strong tendency toward increased mortality in patients under LTOT, but the samples were too small to definitely conclude.

The impact of LTOT prescription outside the guidelines on mortality risk thus needs to be clarified. Conducting a specific RCT would be costly and challenging. In this context, the completion of a systematic review and meta-analysis remains a relevant alternative. Although very few studies aimed to specifically address the association between LTOT outside the guidelines and mortality in COPD, re-analysis of available datasets is a possible option. Indeed, in the literature, PaO_2 data and oxygen therapy status are almost systematically reported for each patient to characterise the severity of COPD. In the studies which also assessed mortality, it will be possible to carry out re-analyses in order to verify whether the mortality rates evolve differently according to the association of PaO_2 and LTOT. Individual participant data meta-analysis (IPD-MA) is a reliable and relevant tool to address this question in the present context. Performing

an IPD-MA requires synthesis of patient-level data across multiple studies. Those kind of meta-analyses are considered as gold-standard for several reasons: (1) they allow greater statistical flexibility to control for individual variability compared with aggregate meta-analysis, which can only account for variance at the study level,[31] (2) statistical analyses can be adapted to consistently accommodate the features of the data from each study and differences in study setting (inclusion/exclusion criteria, missing data, differences for measuring effect size, time effect, etc) and (3) potential statistical bias or poorly reported outcomes from individual study can be verified and modelled in a more appropriate way (see Riley *et al*[32] for further advantages).

OBJECTIVES OF THE IPD-MA

This project will address this specific question: does LTOT provided outside the guidelines (ie, in patients without severe hypoxaemia) increase the HR of death in patients with COPD? Given the reported adverse effects of supplemental oxygen therapy at high oxygenation targets in the acute settings, we hypothesise that patients with COPD chronically exposed to supplemental oxygen therapy at high oxygenation targets (ie, patients who are prescribed LTOT outside the guidelines) have a higher HR of death compared with patients with COPD under LTOT in line with the guidelines or all patients with COPD without LTOT (outside or in line with the guidelines).

To address the question, relevant studies combining a measure of hypoxaemia degree, survival status and LTOT status among patients with COPD will be identified through a systematic review. Then, the datasets of selected studies will be analysed to compare the association between LTOT and mortality in patients with COPD as a function of hypoxaemia severity.

METHODS AND ANALYSES

Patient and public involvement

No patient involved.

Registration

The protocol was designed in accordance with the PRISMA-IPD guidelines[33] and is registered on the PROSPERO database.

Eligibility criteria for selected studies

Types of studies

All retrospective or prospective cohort studies from any countries and published in English or French languages with no date restriction will be included. Databases from unpublished studies and not yet published studies but meeting inclusion criteria might be included in the study. Thus, by openly publishing this protocol, the authors also invite all readers with such databases to share them in order to contribute to the project. In addition, the protocol will be shared with specific research networks working on the study topic.

Population

The subjects of the selected studies will have to be older than 40 years with a COPD diagnosis, defined as a documented forced expiratory volume in the first second of forced expiration (FEV_1)/forced vital capacity (FVC) ratio <0.70 after bronchodilator intake. In addition, the studies will have to verify the following four conditions:

- Cohort of stable COPD (last exacerbation >4 weeks) at the moment of the study.
- Partial arterial oxygen values data during breathing ambient air in resting conditions available
- Indication of the presence or absence of LTOT (ie, prescription of at least 15 hours/day) filled out at the moment of the study.
- Survival follow-up, without any time restriction on the follow-up duration

Exclusion criteria

Cohorts with specific selection of subgroup of patients based on hypoxaemia severity (eg, studies only focusing on severe hypoxaemia and studies including only patients with normoxaemic COPD) will not be included.

Interventions/exposure and comparator groups

The exposure group will be stable patients with COPD with LTOT despite not meeting the LTOT prescription criteria (ie, patients with a PaO_2 higher than 59 mm Hg at the time of the prescription or/and at the time of inclusion in the study).

Three comparator groups will be investigated:

- Stable patients with COPD with LTOT prescription who meet the LTOT prescription criteria (ie, PaO_2 less than 55 mm Hg or less than 59 mm Hg with concurrent polycythaemia or signs of right-sided heart failure or pulmonary hypertension),
- Stable patients with COPD without LTOT prescription and who do not meet the prescription criteria (ie, PaO_2 higher than 59 mm Hg or PaO_2 between 55 mm Hg and 59 mm Hg without concurrent polycythaemia or signs of right-sided heart failure or pulmonary hypertension),
- Stable patients with COPD without LTOT prescription despite meeting the LTOT prescription criteria (ie, PaO_2 less than 55 mm Hg or less than 59 mm Hg with concurrent polycythaemia or signs of right-sided heart failure or pulmonary hypertension).

Types of outcome measures

We will include studies that report the time to death (all-cause mortality).

Exclusion criteria

We will exclude book chapters and systematic reviews (but reference lists will be checked as mentioned above).

PICOS summary

The criteria for including studies in the review can be as summarised in table 1.

Table 1 PICOS summary

Population	Intervention/exposure	Comparator	Outcomes	Setting
Patients with COPD (>40 years old). In addition, the studies will have to verify the following 4 conditions: ► Cohort of stable COPD (last exacerbation >4 weeks) at the moment of the study. ► Partial arterial oxygen values data during breathing ambient air in resting conditions available. ► Indication of the presence or absence of LTOT (ie, prescribed at least 15 hours/day) filled out at the moment of the study. ► Survival follow-up for at least 12 months after the inclusion in the study	Patients with LTOT	Patients without LTOT	Mortality (time to death)	Retrospective cohort studies and prospective cohort studies

COPD, chronic obstuctive pulmonary disease; LTOT, long-term oxygen therapy.

Study outcomes

The main outcome for the IPD-MA will be time to death. The time to death will be calculated as the number of days between the date of inclusion in the selected study or, if available, from oxygen prescription (index date) to death or end date of studies, which ever came first. The survival times of patients still alive will be censored at the date of last follow-up.

Moderator analyses

Characteristics of the patients (patient-level moderators)

The following covariates known to influence mortality in COPD will be integrated in the analyses: age, sex, body mass index (BMI), arterial carbon dioxide tension ($PaCO_2$), exercise tolerance (6-minute walking distance), dyspnoea (modified Medical Research Council (mMRC) score), comorbidities (COPD-specific co-morbidity test (COTE) index), FEV_1 and the presence of at least one of the following three conditions: polycythaemia or signs of right-sided heart failure or pulmonary hypertension.

Characteristics of the studies (study-level moderators)

Time: timing of outcome and time of follow-up will also be assessed and will be considered for mortality analyses since timeframes will be different between studies. An important source of heterogeneity is length of follow-up as this may impact the hazard of death. These aspects will be carefully detailed during the review process and controlled for in our analyses (eg, by running a moderator analysis with the length of follow-up as a continuous variable or, if few variability is found for this outcome, by performing subgroup analyses for each length of follow-up).

Data collection

Search strategy and methods for the identification of studies

The protocol was prepared according to the guidelines of the Preferred Reporting Items for a Systematic Review and Meta-Analyses of IPD (PRISMA-IPD) Development Group.[33] A multistage search strategy will be completed to identify all potential datasets (figure 1). Literature search strategies will be developed using text words for all databases or using medical subject headings (MeSH for MEDLINE) related to COPD–LTOT–survival–follow-up study. MEDLINE (PubMed platform), Web of Science, EMBASE and Cochrane Central Register of Controlled Trials bibliographic databases will be searched from database inception to the present day. ClinicalTrial registry will also be searched to identify any unpublished trial. Authors of these trials will be contacted via email and invited to share unpublished data. Databases with unpublished data will be checked and details (eg, origin, context of data collection, etc) will be then specified. Finally, articles from grey literature and from preprint will be searched on OpenGrey platform (http://www.opengrey.eu/) and BioRxiv/MedRxix platforms (https://www.biorxiv.org and https://www.medrxiv.org, respectively). Bibliography of eligible articles as well as existing systematic reviews in the field will also be screened. Extra studies or datasets not found after databases searching but meeting inclusion criteria will be included through a snowballing search. Subsequently, the authors of eligible studies will be contacted and asked to share IPD.

Screening, study selection and electronic database of the study

For each database, registry and resources platform, searching will be conducted using different strategy steps and different combinations of searching terms (see online supplemental appendix 1).

Study selection will be performed by two authors (FA and VM). They will independently screen the titles and abstracts of retrieved studies identified by the search strategies and if these meet inclusion criteria. Following the initial identification and removal of duplicates, these potentially eligible studies will be re-evaluated in the full text by two authors (FA and VM) for inclusion criteria checking defined previously. Disagreements will be resolved through discussion and if not, a third author (NH) will decide.

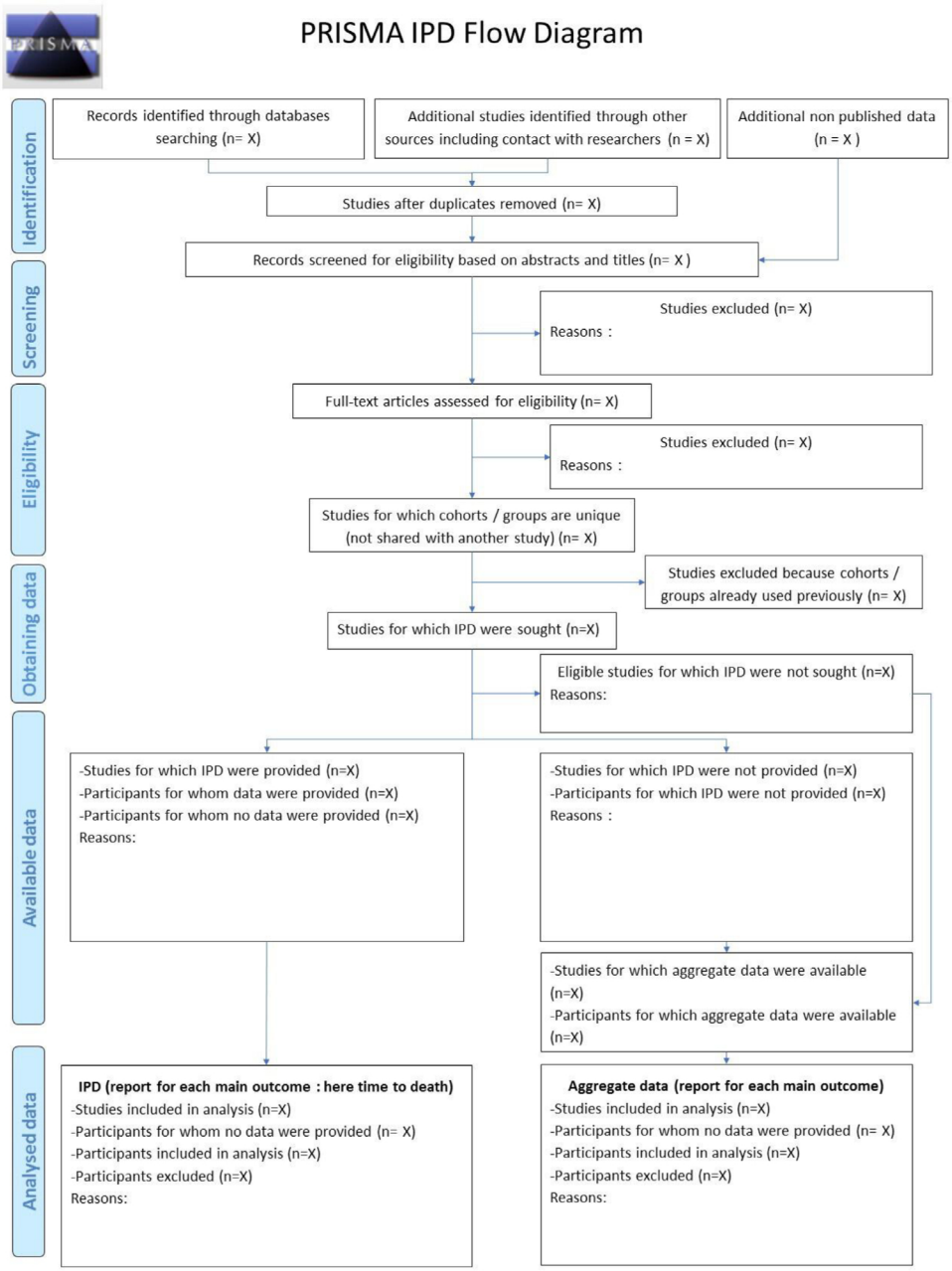

Figure 1 PRISMA-IPD flow diagram. PRISMA-IPD, Preferred Reporting Items for a Systematic Review and Meta-Analyses of Individual Participant Data.

Data extraction and management

Study selection procedure will be presented in a PRISMA-IPD flow diagram (figure 1). The final results from the literature search will be downloaded and saved into the Zotero reference management software. Data will be extracted onto a datasheet by one author and later checked for accuracy by a second author. Extracted data will include study characteristics (title, corresponding authors' contact details, publication year, journal and type of study), population characteristics (number of patients with COPD, age and sex ratio), characteristics of the intervention and comparator and the different sought outcomes. Once the studies will be selected and extracted, corresponding authors of the identified eligible published studies and trials will be contacted via email with a cover letter, or in a personal conversation, detailing the objectives of the collaborative meta-analysis, background information and the datasheet for input of individual patient results for the project. Indeed, those responsible for the included studies will be asked to supply individual participant data comprising de-identified participants reference. Moreover, owners of unpublished selected databases will be contacted in the same manner.

A master database will be created grouping all respective datasheets and each study will have an ID number. If some IPD characteristics or outcomes are missing, unclear or not existent in the dataset provided, we will

Table 2 Individual data requested to authors for IPD-MA

Patient-level data			
Study parameters	**Patient details**	**Intervention/treatment**	**Outcomes**
Follow-up time period	► Sex ► Age ► FEV_1 (L) ► Tiffeneau index (FEV_1/FVC) ► PaO_2 (mm Hg) ► $PaCO_2$ (mm Hg) ► BMI ► Comorbidities	LTOT (ie, prescribed at least 15 hours/day) at the inclusion time	► Vital status at publication time ► Death date
Study-level data			
► Country of completion ► Date of publication ► Methodological quality of study ► Reasons for missing data			

BMI, body mass index; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; IPD-MA, individual patient data meta-analysis; LTOT, long-term oxygen therapy; $PaCO_2$, arterial carbon dioxide tension; PaO_2, arterial oxygen tension.

report them in study limitations. All IPD will be saved on a secure server. IPD integrity: individual datasets will be checked for missing, invalid, out of range or inconsistent items.

Risk of bias and quality assessment

Risk of bias and quality assessment will be carried out independently by two researchers for each included study using the Newcastle Ottawa Scale (NOS) for cohort studies[34] (see online supplemental appendix 2). The NOS contains eight questions allowing to assess information bias, selection bias and confounding in cohort studies. Study will be graded as being of good, fair or poor quality.[35] Disagreements will be resolved by discussion between the two reviewers. If a risk of bias for a study remains unclear, corresponding authors of each study could be asked to provide additional information to resolve the uncertainty.

Individual participant data meta-analysis

Data items

The different data types which will be requested are mentioned in table 2.

Statistical analyses

The conduct and reporting of this IPD-MA will rely on the PRISMA-IPD statement[33] and following the recommendations of a specific statistical tutorial for this kind of analyses.[36] A one-step IPD-MA will be conducted to study the association between oxygen therapy and hazard of death using multilevel survival analyses using Cox-mixed effects models with two levels structure (patient and study) will be performed. Subgroup analyses will be run to identify the role of each potential moderators described above (ie, age, gender, BMI, $PaCO_2$, comorbidities, FEV_1 and the presence of at least one of the following condition: polycythaemia or signs of right-sided heart failure or pulmonary hypertension). Missing data will be described but no imputation will be performed, as it is recommended for that kind of analysis.[37] According to the method described in Austin,[36] the following R packages will be used: survival, lme4 and coxme. All statistical analyses will be independently replicated by one of the co-authors and an external collaborator. Data and codes will be made available online on medRxiv Data Repository at the time of the submission.

ETHICS AND DISSEMINATION

This paper contains the original study protocol. Any substantial modifications to the protocol will be listed and justified in a supplementary document according to the PRISMA Protocols 2015 guidelines. These amendments will be documented in detail in the PROSPERO Register and will be described transparently. Only studies that have received institutional approval from an ethics committee and present anonymised IPD will be included in the meta-analysis. As this is a protocol for a systematic review, an ethics committee review is not required. A data sharing agreement will be signed between the authors of included studies and the IPD-MA research team. The resulting IPD-MA dataset will be shared and made publicly available through the medRxiv Data Repository (accessed via https://www.medrxiv.org/) in accordance with open-science practices. Results will be disseminated via scientific forums, including peer-reviewed publications and presentations at international conferences.

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Contributors VM is the guarantor of the review. FA, NH and VM designed the project. FA, GC, MH, NH, VM, GM and AV contributed to study methods, writing the paper, read and approved the final version of the manuscript for submission.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. There is no data available related to this protocol.

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