An adjudication algorithm for respiratory-related hospitalisation in idiopathic pulmonary fibrosis

Paul Ford[1], Michael Kreuter[2], Kevin K. Brown[3], Wim A. Wuyts[4], Marlies Wijsenbeek[5], Dominique Israël-Biet[6], Richard Hubbard[7], Steven D. Nathan[8], Hilario Nunes[9], Bjorn Penninckx[1], Niyati Prasad[1], Ineke Seghers[1], Paolo Spagnolo[10], Nadia Verbruggen[1], Nik Hirani[11], Juergen Behr[12], Robert J. Kaner[13] and Toby M. Maher[14,15]

[1]Galapagos NV, Mechelen, Belgium. [2]Center for Pulmonary Medicine, Departments of Pneumology, Mainz University Medical Center and of Pulmonary, Critical Care and Sleep Medicine, Marienhaus Clinic Mainz, Mainz, Germany. [3]Department of Medicine, National Jewish Health, Denver, CO, USA. [4]Unit for Interstitial Lung Diseases, Department of Respiratory Medicine, University Hospitals Leuven, Leuven, Belgium. [5]Centre for Interstitial Lung Disease and Sarcoidosis, Department of Respiratory Medicine, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands. [6]Université Paris Cité, Hôpital Européen Georges Pompidou, Paris, France. [7]Academic Unit of Population and Lifespan Sciences, School of Medicine, University of Nottingham, Nottingham, UK. [8]Inova Advanced Lung Disease and Transplant Program, Inova Fairfax Hospital, Falls Church, VA, USA. [9]Department of Pneumology, Centre de Référence des Maladies Pulmonaires Rares, Assistance Publique–Hôpitaux de Paris, Hôpital Avicenne, Université Sorbonne Paris Nord, Bobigny, France. [10]Respiratory Disease Unit, Department of Cardiac, Thoracic, Vascular Sciences and Public Health, University of Padova, Padova, Italy. [11]Edinburgh Lung Fibrosis Clinic, Royal Infirmary Edinburgh and Centre for Inflammation Research, The Queen's Medical Research Institute, The University of Edinburgh, Edinburgh, UK. [12]Department of Medicine V, LMU University Hospital, Ludwig Maximilian University Munich, Comprehensive Pneumology Center (member of the German Center for Lung Research), Munich, Germany. [13]Division of Pulmonary and Critical Care Medicine and Department of Genetic Medicine, Weill Cornell Medicine, New York, NY, USA. [14]National Heart and Lung Institute, Imperial College London, London, UK. [15]Keck Medicine of University of Southern California, Los Angeles, CA, USA.

Corresponding author: Toby M. Maher (Toby.Maher@med.usc.edu)

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This algorithm for the adjudication of respiratory-related hospitalisation in IPF clinical trials will help achieve consistency in the reporting of this end-point, increasing comparability of data
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Abstract

Background There is no standard definition of respiratory-related hospitalisation, a common end-point in idiopathic pulmonary fibrosis (IPF) clinical trials. As diverse aetiologies and complicating comorbidities can present similarly, external adjudication is sometimes employed to achieve standardisation of these events.

Methods An algorithm for respiratory-related hospitalisation was developed through a literature review of IPF clinical trials with respiratory-related hospitalisation as an end-point. Experts reviewed the algorithm until a consensus was reached. The algorithm was validated using data from the phase 3 ISABELA trials (clinicaltrials.gov identifiers NCT03711162 and NCT03733444), by assessing concordance between nonadjudicated, investigator-defined, respiratory-related hospitalisations and those defined by the adjudication committee using the algorithm.

Results The algorithm classifies respiratory-related hospitalisation according to cause: extraparenchymal (worsening respiratory symptoms due to left heart failure, volume overload, pulmonary embolism, pneumothorax or trauma); other (respiratory tract infection, right heart failure or exacerbation of COPD); "definite" acute exacerbation of IPF (AEIPF) (worsening respiratory symptoms within 1 month, with radiological or histological evidence of diffuse alveolar damage); or "suspected" AEIPF (as for "definite" AEIPF, but with no radiological or histological evidence of diffuse alveolar damage). Exacerbations ("definite" or "suspected") with identified triggers (infective, post-procedural or traumatic, drug toxicity- or aspiration-related) are classed as "known AEIPF"; "idiopathic AEIPF" refers to exacerbations with no identified trigger. In the ISABELA programme, there was 94% concordance between investigator- and adjudication committee-determined causes of respiratory-related hospitalisation.

Conclusion The algorithm could help to ensure consistency in the reporting of respiratory-related hospitalisation in IPF trials, optimising its utility as an end-point.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive lung disease that places a high burden on patients, with excessive mortality and increasing prevalence [1, 2]. Pirfenidone and nintedanib are approved for the treatment of IPF [3, 4], but neither reverse existing pathology [5–7]. Novel therapeutic agents are under development [8], leading to a pressing need to optimise and standardise clinical trial end-points [9].

Respiratory-related hospitalisation is common in individuals with IPF. In a 5-year follow-up study, 87% of patients with IPF were hospitalised at least once, with 37% of hospitalisations due to acute respiratory worsening [10]. Each year in the UK alone, there are an estimated 9000 hospital admissions due to IPF [11], and 5–14% of patients in a typical IPF clinical trial are hospitalised during the study [12–14]. The financial impact of IPF respiratory-related hospitalisation is significant, with one USA study estimating the mean cost per admission to be USD 16 000 [15]. Respiratory-related hospitalisation is associated with high morbidity and increased mortality, irrespective of the cause of respiratory worsening [14, 16–18]. In a cohort study of 592 patients, median survival was 2.8 months following respiratory-related hospitalisation, compared with 27.7 months following nonrespiratory-related admissions [19]. Data from a large USA medical insurance database showed pirfenidone or nintedanib treatment decreased the risk of all-cause mortality and of acute (mostly respiratory-related) hospitalisation when compared with an untreated IPF matched cohort, supporting the use of respiratory-related hospitalisation as an end-point [20].

Many of the symptoms and clinical features of respiratory-related causes of hospitalisation are nonspecific. For example, worsening dyspnoea could have pulmonary or extrapulmonary causes [21]. Moreover, many patients with IPF have serious comorbidities, such as pulmonary hypertension [22, 23], COPD, lung cancer and heart disease [23]; comorbidity burden is associated with high morbidity and mortality [24]. Owing to this complexity, hospitalisations during IPF treatment trials may be centrally adjudicated to ensure accurate and standardised end-point classification. However, there is currently no universally accepted definition of respiratory-related hospitalisation; thus, there is impetus for the creation of a clear, standardised, pre-determined methodology to define and adjudicate these events.

We developed an algorithm for the adjudication of respiratory-related hospitalisation in IPF trials, based on a literature review and using clinical data available to practicing clinicians [25–28]. The algorithm provides methodology to define types of respiratory-related hospitalisation event, thus confirming respiratory-related hospitalisation. The algorithm was used by a blinded clinical end-point adjudication committee (CEAC) to adjudicate respiratory-related hospitalisation events in two phase-3 IPF trials: ISABELA 1 and 2 (NCT03711162 and NCT03733444) [29]. The concordance between the CEAC and investigators with regards to the cause of respiratory-related hospitalisation was assessed.

Methods

Literature review

A literature review was conducted to identify English-language reports of phase-2 and -3 randomised clinical trials (RCTs) in IPF in which respiratory-related hospitalisation and/or acute exacerbations of IPF (AEIPFs) were pre-specified end-points. To identify articles, the PubMed database was searched for ("idiopathic pulmonary fibrosis" AND "trial" AND ["hospital" OR "acute exacerbation"]). All articles published between 1 January 2000 and 31 October 2018 were retrieved. This process was repeated during the development of this article (with an end date 28 September 2019), to capture full or follow-on publications of studies previously only reported within a clinical trials registry. We identified 322 articles, which was reduced to 128 when further filtered by the inclusion of "clinical trials". When the abstract and/or full text of articles were manually reviewed, 16 RCTs that met the criteria for inclusion and two cohort studies of *post hoc* adjudication of RCTs were identified. Supplementary table S1 summarises the reasons for exclusions.

Additional studies were identified from the reference lists of articles. To identify ongoing studies, the ClinicalTrials.gov database was searched using the terms "idiopathic pulmonary fibrosis" AND "hospital", as well as "idiopathic pulmonary fibrosis" AND "acute exacerbation", filtering for phase-2 and -3 trials (supplementary table S1). Additional identified articles included nine RCTs identified from other sources, eight ongoing RCTs identified on ClinicalTrials.gov and two additional cohort studies identified from other sources. Hence, a total of 33 RCTs and four cohort studies were included.

Algorithm development

An international working group was established, comprising nine expert clinician researchers with experience in adjudicating IPF clinical trials (supplementary table S2). Based on the literature review results, plus flowcharts previously developed for the diagnosis of AEIPF [26, 28], five members of the expert group (P. Ford, K.K. Brown, N. Hirani, J. Behr and R.J. Kaner) developed an algorithm for the adjudication of respiratory-related hospitalisation. The proposed algorithm was circulated to the wider group for review and the algorithm was revised. This process was repeated, and a third version was approved by the whole expert group. This final version was used by the CEAC of the ISABELA trials, which comprised eight members, three of whom were among the experts responsible for developing the algorithm. Details of the ISABELA trials have been reported previously. Study protocols were approved by the independent ethics committee/institutional review board for each site or country, as applicable, and all patients provided written informed consent.

Algorithm validation

The CEAC of the ISABELA studies adjudicated respiratory-related hospitalisation and deaths; the algorithm was used for the adjudication of respiratory-related hospitalisation. If an event causing death and death itself occurred on the same calendar day, then death was the only event classified; death and the event causing death were classified as separate events if they occurred on different calendar days. Events (hospitalisations and deaths regardless of cause) were identified primarily from the completed electronic case report forms reported by site investigators *via* an electronic data capture system. Source documents (listed in supplementary table S3) were then requested from the site to support adjudication of the event by the CEAC. The case was not adjudicated if necessary source documentation for adjudication could not be obtained. Two members of the CEAC independently evaluated each case; a third CEAC member evaluated discrepant cases (agreeing with one of the previous adjudicators or forming an alternative verdict). To validate the algorithm, the cause of hospitalisation as determined by the CEAC using the algorithm (*i.e.* the type of respiratory-related hospitalisation) was compared with the cause stated by the study investigator (provided in narrative form). The proportion of cases in which there was agreement between the CEAC and investigator was recorded. This qualitative comparison was performed by two Galapagos (Mechelen, Belgium) employees. Concordance between the CEAC and the investigators for cause of death was also assessed qualitatively.

Results

Literature review

Respiratory-related hospitalisation

Respiratory-related hospitalisation and AEIPF were used as end-points in the 33 included phase-2 and -3 IPF RCTs [6, 12, 13, 25, 30–60] (table 1). However, the vast majority (16 out of 18) of studies that used respiratory-related hospitalisation as an end-point did not include a specific definition beyond "hospitalisation due to respiratory causes/worsening respiratory symptoms". Fewer than half of studies stated that adjudication was performed, with most relying solely on investigator-defined events. Typically, RCTs did not describe the adjudication process beyond stating that adjudication was performed by a committee blinded to treatment group. Among the most detailed descriptions was that in the ARTEMIS-IPF trial, which stated that an end-point committee adjudicated whether the primary reason for hospitalisation was respiratory, nonrespiratory or elective, and whether the primary diagnosis was acute IPF disease progression, IPF disease progression without acute exacerbation, pneumonia, bronchitis, left heart failure or an alternative respiratory event [12].

The National Heart, Lung, and Blood Institute-sponsored IPF Clinical Research Network (IPFnet) published an article summarising the outcomes of the adjudication process for respiratory-related hospitalisation in the ACE-IPF and PANTHER-IPF trials [30]. Following a review of the available clinical records, the adjudication committee classified a hospitalisation as respiratory-related if worsening respiratory symptoms were considered the main reason for hospitalisation. Out of 36 investigator-reported hospitalisations in ACE-IPF, 28 were adjudicated as respiratory and eight as "other". Out of 57 investigator-reported hospitalisations in PANTHER-IPF, 28 were adjudicated as respiratory and 29 as "other".

Two studies performed *post hoc* classification of respiratory-related hospitalisation using pooled data from the CAPACITY and ASCEND trials [18], and from ACE-IPF, PANTHER-IPF and STEP-IPF [14] (table 2). Durheim *et al.* [14] categorised the following as respiratory-related hospitalisation: AEIPF, pulmonary embolism, respiratory tract infection, pneumothorax, aspiration event, COPD exacerbation, lung transplantation and other respiratory worsening (including increased dyspnoea, hypoxia, respiratory distress and other/unclassifiable acute respiratory worsening).

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TABLE 1 Phase-2 and -3 idiopathic pulmonary fibrosis (IPF) clinical trials that included respiratory-related hospitalisation and/or acute exacerbation of IPF (AEIPF) as a pre-specified end-point

First author, year [reference] (study name) identifier number	Phase	Intervention	Hospitalisation			AEIPF		
			Used as end-point? (secondary unless otherwise specified)	Definition reported?	Adjudicated by committee?	Used as end-point? (secondary unless otherwise specified)	Definition reported?	Adjudicated by committee?
Martinez, 2014 [13] (PANTHER-IPF) NCT00650091	3	Acetylcysteine	ACH RRH	No	Yes; details in de Andrade *et al.* [30]	Incidence	As per Collard *et al.* [25]	Yes; details in de Andrade *et al.* [30]
Raghu, 2013 [12] (ARTEMIS-IPF) NCT00768300	3	Ambrisentan	RRH (CPE)	Yes	Yes; no further details	No	No	No
NCT03573505 [32] (SPIRIT)	2	BG00011	TTF-ACH TTF-RRH	No	No	TTF AEIPF Incidence	No	No
NCT01766817 [33]	2	BMS-986020	RRH (CSE) ACH (CSE)	Not specified	Not specified	Incidence	Yes (supplementary table S4)	Not specified
King, 2011 [34] (BUILD-3) NCT00391443	3	Bosentan	No	No		Incidence (CPE) TTF AEIPF (CSE)	No	No
Raghu, 2015 [35] NCT00786201	2	Carlumab	No	No		TTF AEIPF (CPE)	No Investigators were provided with algorithm for diagnosis and management of AEIPF	Described as either "based on HRCT assessment" or "based on investigator assessment" HRCT assessments were adjudicated if required
Naccache, 2019 [36] (EXAFIP study protocol) NCT02460588	3	Cyclophosphamide +corticosteroids	No			Incidence (primary end-point)	As per Collard *et al.* [25]	No
Rosas, 2018 [37] NCT01214187	2	Inhaled carbon monoxide	ACH	No	No	Incidence	As per Collard *et al.* [25]	No
NCT01890265 [38]	2	FG-3019	RRH	No	No	Not specified	No	No
NCT03725852 [39] (PINTA)	2	GLGP1205	TTF-ACH TTF-RRH	No	No	No		
Maher, 2018 [41] (FLORA) NCT02738801	2a	GLPG1690	No			Incidence (safety end-point)	No	
Daniels, 2010 [42] NCT00131274	2	Imatinib	RRH (safety end-point)	No	No	Incidence (safety end-point)	No	No
King, 2009 [43] (INSPIRE) NCT00075998	3	Interferon-γ-1β	Survival days without RRH	No	No	Incidence	No	No
Raghu, 2018 [44] (WRAP-IPF) NCT01982968	2	Laparoscopic antireflux surgery	RRH ACH	No	No	Incidence	As per protocol	"Adjudicated (definitive *versus* suspected) by site investigators according to international working group perspectives"
NCT01872689 [45]	2	Lebrikizumab ±pirfenidone	RRH TTF-RRH ACH (CSE)	No	No	Incidence TTF AEIPF	Yes (supplementary table S4)	No
Raghu, 2013 [46] (MUSIC) NCT00903331	2	Macitentan	No			TTF AEIPF (CSE)	No	No
Richeldi, 2011 [47] (TOMORROW) NCT00514683	2	Nintedanib	No			Incidence	No	No

Continued

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TABLE 1 Continued

First author, year [reference] (study name) identifier number	Phase	Intervention	Hospitalisation			AEIPF		
			Used as end-point? (secondary unless otherwise specified)	Definition reported?	Adjudicated by committee?	Used as end-point? (secondary unless otherwise specified)	Definition reported?	Adjudicated by committee?
Richeldi, 2014 [6] (INPULSIS 1) NCT01335464 (INPULSIS 2) NCT01335477	3	Nintedanib	No			TTF AEIPF	Yes; as per protocol published with article (supplementary table S4) and as per Collard *et al.* [25]	Yes; no further details
Crestani, 2019 [48] (INPULSIS-ON) NCT01619085	Open-label extension of INPULSIS	Nintedanib	No			TTF AEIPF (exploratory end-point)	Yes (supplementary table S3)	No
NCT01979952 [49]	3	Nintedanib	RRH at 6 months	No	No	No		
Raghu, 2018 [50] NCT02550873	2	Pentraxin 2 (human recombinant)	RRH (safety end-point)	Yes (supplementary table S4)	No	"Respiratory decline events" (safety end-point)	Yes (supplementary table S4) and as per Collard and co-workers [25, 28]	No
Huang, 2015 [51] NCT02136992	2	Pirfenidone	No			AEIPF (CSE)	No	No
Azuma, 2005 [52]	3	Pirfenidone	No			Incidence	Yes (supplementary table S4)	No
Noble, 2011 [40] (CAPACITY1) NCT00287729 (CAPACITY2) NCT00287716	3	Pirfenidone	TTF-RRH (CSE)	No	No	TTF AEIPF (CSE)	As per protocol	No
Nishiyama, 2010 [53] JAPICCTCI-050121	3	Pirfenidone	No			Incidence (tertiary end-point)	As per "previous reports and revised criteria for AEIPF in Japan"	No
NCT02951429 [54]	2	Pirfenidone± sildenafil	RRH (CPE and CSE) RRH ACH	No	No	No		
Raghu, 2012 [55] (PANTHER-IPF) NCT00650091	3	Prednisone, azathioprine and N-acetylcysteine	ACH, including as composite end-point (safety end-point)	No	Yes; further details in de Andrade *et al.* [30]	Incidence	As per Collard *et al.* [25]	Yes; further details in de Andrade *et al.* [30]
NCT01969409 [56]	2	Rituximab	ACH	No	No	Incidence	As per consensus criteria (supplementary table S4)	No
Zisman, 2010 [57] (STEP-IPF) NCT00517933	3	Sildenafil	ACH (safety end-point)	No	No	Incidence (safety end-point)	Yes (supplementary table S4)	Yes (supplementary table S4)
Raghu, 2017 [31] NCT01769196	2	Simtuzumab	RRH ACH (*post hoc*)	No	Yes; no further details	Incidence	As per protocol; yes (supplementary table S4)	Yes (supplementary table S4)
NCT03832946 [58]	2	TD139	TTF-ACH TTF-RRH	No	No	No		
Parker, 2018 [59] NCT01629667	2	Tralokinumab	RRH	No	Yes; no further details	RRH due to AEIPF	No	Yes; no further details
Noth, 2012 [60] (ACE-IPF) NCT00957242	3	Warfarin	ACH (CPE) RRH; ACH	No	Yes; further details in de Andrade *et al.* [30]	Incidence	No	Yes; further details in de Andrade *et al.* [30]

ACH: all-cause hospitalisation; RRH: respiratory-related hospitalisation; CPE: composite primary end-point; TTF: time-to-first; CSE: composite secondary end-point; HRCT: high-resolution computed tomography.

TABLE 2 Cohort studies that performed *post hoc* adjudication of respiratory-related hospitalisation outcomes in phase-2/3 idiopathic pulmonary fibrosis (IPF) randomised controlled trials

First author, year [reference] (study name) identifier number	Definition	Adjudication process
Durheim, 2015 [14] (STEP-IPF, ACE-IPF, PANTHER-IPF) NCT00650091 NCT00517933 NCT00957242	Classified the following as respiratory-related causes of hospitalisation: AEIPF PE RTI Pneumothorax Aspiration event COPD exacerbation Lung transplantation Other respiratory worsening (increased dyspnoea, hypoxia, respiratory distress, other/unclassifiable acute respiratory worsening)	ACE-IPF, STEP-IPF and PANTHER-IPF: IPFnet investigators adjudicated outcomes centrally *via* teleconference STEP-IPF: adjudication process included review of records by ⩾2 clinicians, a radiologist and a pathologist, followed by a telephone discussion until consensus was achieved
Ley, 2017 [18] (CAPACITY1, CAPACITY2, ASCEND) NCT00287729 NCT00287716 NCT01366209	"In CAPACITY, hospitalisation was a pre-specified secondary end-point, and the local site investigator selected the primary reason for hospitalisation from among acute respiratory decompensation; IPF exacerbation; pneumonia; respiratory related, other; or non-respiratory related" "In ASCEND, hospitalisation was recorded as an SAE"	All hospitalisations in the CAPACITY trials, except those in the "non-respiratory related" category, were classified as respiratory-related All hospitalisations in ASCEND were independently reviewed by two experienced pulmonologists blinded to treatment and were categorised as either respiratory related or non-respiratory related. Discordance (n=1) was independently adjudicated by a third experienced pulmonologist blinded to treatment

AEIPF: acute exacerbation of IPF; PE: pulmonary embolism; RTI: respiratory tract infection; SAE: serious adverse event.

AEIPF

The majority (28 out of 32) of RCTs included AEIPF as an end-point, reporting the proportion of patients affected and/or the time-to-first AEIPF (table 1). Fewer than half of studies stated that central adjudication was used to distinguish between definite and suspected AEIPF events. Approximately one-third of studies reported that AEIPF was defined using the consensus criteria proposed by Collard and co-workers [25, 28], with a minority reproducing the criteria they used in full (supplementary table S4). Several further studies stated that AEIPF was defined in the study protocol, but the protocol was not available.

IPFnet published details of the adjudication process for AEIPF in the ACE-IPF, PANTHER-IPF and STEP-IPF trials [30]. The definition of AEIPF used by IPFnet was based on the consensus criteria published by Collard *et al.* [25]. All suspected AEIPFs were referred to the adjudication committee. Events were classified as "definite acute worsening" (all criteria met, no alternative aetiology), "unclassifiable acute worsening" (insufficient data to evaluate all criteria, no alternative aetiology) or "not acute exacerbation" (alternative aetiology identified that explained the acute worsening) (refer to supplementary table S4 for stated criteria). The committee adjudicated 88 suspected AEIPF events; 29 were judged as definite and 31 as unclassifiable. Of the unclassifiable cases, 75% were missing a computed tomography scan, 10% were missing data on infection status and in 15% the data were too ambiguous to reach a definite conclusion.

In a *post hoc* analysis of the INPULSIS trials, fewer than two-thirds of investigator-reported AEIPFs were judged by retrospective central adjudication as AEIPFs [61, 62] (table 3). Out of 79 investigator-reported AEIPFs, the adjudication committee rated nine (11%) to be correct AEIPFs and 33 (42%) to be suspected acute exacerbations; 35 (44%) were not considered acute exacerbations, and two could not be adjudicated because of insufficient data [61]. A similar pattern emerged in a second analysis, in which 31 (63%) out of 49 serious adverse events reported by trial investigators were judged by adjudication to be a confirmed/suspected AEIPF, whereas 18 (37%) out of 49 were deemed "not an AEIPF" [62]. For 14 investigator-reported nonserious adverse events deemed to be AEIPFs, the adjudication committee found five (36%) to be confirmed/suspected AEIPFs; nine (64%) were "not an AEIPF".

Respiratory-related hospitalisation algorithm

The algorithm we developed (figure 1) builds on the most recent consensus-based recommendations for AEIPF diagnosis [25–28] and the findings from the literature review. It incorporates additional decision

TABLE 3 Cohort studies that performed *post hoc* adjudication of acute exacerbation events in phase-2/3 idiopathic pulmonary fibrosis (IPF) randomised controlled trials

First author, year [reference] (study name) identifier number	Definition	Adjudication process
Kreuter, 2019 [62] (INPULSIS 1 and 2) NCT01335464 NCT01335477	As per protocol	"Adverse events were adjudicated by a committee of three experts blinded to treatment assignment as a confirmed acute exacerbation (if all protocol-defined criteria were met), a suspected acute exacerbation (if the event was felt to be an acute exacerbation but did not meet all protocol-specified criteria) or not an acute exacerbation (if an alternative cause was identified)" Out of 49 investigator-reported SAEs deemed by the investigator to be AEIPFs, 31 (63%) were adjudicated as being a confirmed/suspected AEIPF, and 18 (37%) were adjudicated as "not an AEIPF" Of 14 investigator-reported non-SAEs deemed by the investigator to be AEIPFs, five (36%) were adjudicated as being a confirmed/suspected AEIPF, and nine (64%) were adjudicated as "not an AEIPF"
Collard, 2017 [61] (INPULSIS 1 and 2) NCT01335464 NCT01335477	As per protocol	"The adjudication committee comprised three experts in IPF who were not investigators in the INPULSIS trials. An event was adjudicated as a 'confirmed acute exacerbation' if all the protocol-defined criteria were met, a 'suspected acute exacerbation' if the event was felt to be an acute exacerbation but failed to meet all protocol-specified criteria, or 'not an acute exacerbation' if an alternative cause was identified" Out of the 79 investigator-reported AEIPFs, nine (11%) were adjudicated as confirmed acute exacerbations, 33 (42%) as suspected acute exacerbations and 35 (44%) as not acute exacerbations. For two events, insufficient data were available for adjudication Mortality was similar following investigator-reported acute exacerbations, adjudicated confirmed/suspected acute exacerbations and events adjudicated as not acute exacerbations

SAE: serious adverse event; AEIPF: acute exacerbation of IPF.

points to capture other (non-AEIPF) respiratory-related causes of hospitalisation. In brief, all patients hospitalised because of increasing pulmonary symptoms should undergo nonenhanced, high-resolution computed tomography to distinguish parenchymal from extraparenchymal causes. If chest imaging combined with other clinical data suggests something other than AEIPF (typical signs of acute exacerbation not identified) and indicate that extraparenchymal causes can be excluded, the classification "other cause of respiratory hospitalisation" is assigned. Note that in the absence of significant left ventricular dysfunction in a patient with IPF, right-sided heart failure is considered a respiratory cause.

In patients with worsening respiratory symptoms within the past month, for whom chest imaging and other clinical data are compatible with AEIPF, the hospitalisation is rated to be due to "AEIPF". This is further classified as "definite AEIPF" when all criteria are met (there is radiological or histological evidence of diffuse alveolar damage), with all other cases classed as "suspected AEIPF". If the trigger for AEIPF (which may be infective, post-procedural, traumatic, drug toxicity-related or aspiration-related) is identified, the cause of hospitalisation is classified as "known AEIPF" (*i.e.* triggered AEIPF) and, if not, as "idiopathic AEIPF". This applies for both "definite" and "suspected" AEIPF.

"Extraparenchymal" cases (table 4), "other respiratory" and all cases of "AEIPF" (definite or suspected; known trigger or idiopathic) are considered "respiratory causes of hospitalisation". All other hospitalisations are classified as "nonrespiratory". Note that the algorithm excludes elective hospital admission for lung transplantation.

Algorithm validation

A total of 349 respiratory-related hospitalisations were identified for adjudication in the ISABELA studies. Overall, 338 (97%) out of 349 hospitalisations were adjudicated by the CEAC using the algorithm; the remaining 11 (3%) were not adjudicated due to insufficient data. Among adjudications, the rate of disagreement between the first and second adjudicator was 30%; in these instances a third CEAC member decided the cause of hospitalisation. The third adjudicator reached a different verdict to either of the two previous adjudicators in 10.7% of cases. Discordance between the CEAC (using the algorithm) and study investigators (reporting a case narrative) occurred in 21 (6.2%) out of 338 adjudicated cases. Four Galapagos representatives checked discordant cases for commonalities to potentially inform improvements

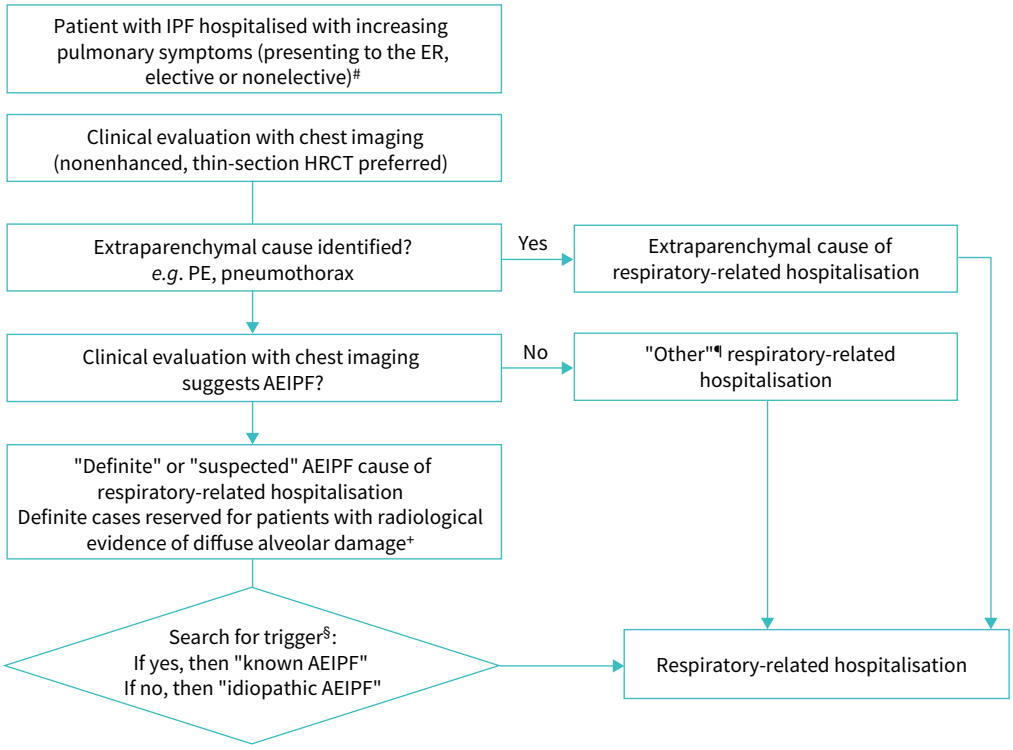

FIGURE 1 Algorithm for the adjudication of respiratory-related hospitalisation in idiopathic pulmonary fibrosis (IPF). For simplicity, "extraparenchymal" and "other respiratory" are both considered respiratory causes of hospitalisation, together with acute exacerbation of IPF (AEIPF) ("definite" or "suspected", in which both are either "known" (*i.e.* known trigger) or "idiopathic"). All other admissions are "nonrespiratory" and classed as such. ER: emergency room; HRCT: high-resolution computed tomography; PE: pulmonary embolism. #: elective (nonemergency) admission to hospital for lung transplantation is excluded. ¶: rule out primary cardiac causes (*e.g.* congestive cardiac failure, myocardial infarction, arrhythmia); if no significant left ventricular dysfunction, right-sided heart failure is considered a respiratory cause. +: if no evidence of diffuse alveolar damage, the case is suspected. §: exacerbations with identified triggers (infective, post-procedural or traumatic, drug toxicity-related or aspiration-related) are classed as "known AEIPF"; those with no identified trigger are classed as "idiopathic AEIPF".

in the algorithm; however, no events were more prevalent than others (no events were particularly conflictual). Furthermore, there was no substantial overlap between cases that were discordant and cases that were adjudicated differently by CEAC members.

When respiratory-related hospitalisation and deaths were considered together, 427 cases were identified for adjudication. A total of 416 (97%) out of 427 hospitalisations and deaths were adjudicated (11 cases were not adjudicated due to insufficient data). The CEAC adjudicators disagreed in 34% of their evaluations, requiring a final decision by a third CEAC member, who reached a different verdict to either of the two previous adjudicators in 10.5% of cases. Discordance between the CEAC and study investigators occurred in 44 (10.6%) out of 416 cases. Data regarding nonagreement between CEAC members were assessed to see whether there was a learning effect with repeated algorithm use. When the assessment period was divided into two sequential periods (August 2019 to mid-June 2020 and mid-June 2020 to May 2021),

TABLE 4 Examples of extraparenchymal causes of respiratory-related hospitalisation

Left-sided heart failure
Pleural effusion
Pneumothorax
Pulmonary embolism
Trauma
Volume overload

internal CEAC disagreement occurred in 24% and 37% of cases in the first and second periods, respectively. There were no differences in the type of event to occur between the two periods. When the total number of cases assessed (n=416) was divided into two, CEAC disagreement occurred in 31% and 38% of the first and last 208 cases, respectively. These findings indicate that algorithm use did not improve over time.

Discussion

Findings from the literature review showed that respiratory-related hospitalisation was not defined nor adjudicated in the majority of studies, and while the development of standardised criteria for AEIPF [25–28] has improved the reliability of AEIPF classification, the complexity of diagnosis means that central adjudication is still required. The diagnostic ambiguity associated with respiratory-related end-points in IPF highlights the need for an algorithm for respiratory-related hospitalisation adjudication.

Adjudication will impose additional requirements and costs (*e.g.* a formal adjudication committee with regular training in the use of the algorithm, alongside access to complete medical records). In the ISABELA trials, an electronic system was used to maximise efficiency. In instances of missing data, an adjudication committee may request additional information from investigators to determine the nature of the hospitalisation and more accurately categorise the event.

The algorithm was developed by experts in the USA and Western Europe; resource availability, clinical practice and opinion may vary in other regions, *e.g.* in Asia where acute exacerbations are more frequent, with perhaps more devastating outcomes [31, 63, 64]. Therefore, the algorithm was purposefully designed to be simple to help minimise discordance and ensure that the clinical data required are available to most clinicians. This will also help ensure that differences between sites and countries with respect to, for example, the imaging equipment available, will not impede application of the algorithm. Developing a simple algorithm for a complex end-point is not without its challenges and we acknowledge that some difficulties related to terminology may remain. For example, a documented viral infection could be classed as pneumonia or triggered acute exacerbation.

As there is no generally accepted, gold-standard definition for respiratory-related hospitalisation, it is not possible to compare the algorithm with a current standard. However, comparisons can be drawn with reported definitions of AEIPF. The definition used by IPFnet states that AEIPF includes “unexplained worsening of dyspnoea or cough within 30 days” [30], whereas our algorithm uses the broader AEIPF criterion of worsening respiratory symptoms within the past month. In addition, the IPFnet definition requires both “new superimposed ground-glass opacities or consolidation on computed tomography scan, or new alveolar opacities on chest radiograph”, a “decline of $\geqslant$5% in resting room air oxygen saturation by pulse oximetry from last recorded level or decline of $\geqslant$8 mmHg in resting room air partial pressure of oxygen from last recorded level” and a lack of clinical and microbiological evidence of infection [30]. In IPFnet studies, cases were adjudicated as “unclassifiable acute worsening” when these criteria were not met, or insufficient data were available (*e.g.* missing imaging, oxygen saturation or partial pressure of oxygen data). Our algorithm uses broader criteria to classify “definite” AEIPF and allows cases of “suspected” AEIPF to be recorded as such; thus, it may be more practical to apply and less likely to incorrectly classify those with AEIPF due to missing radiological or physiological data.

The algorithm was used to adjudicate events in the ISABELA studies. There was a high rate of agreement between investigator- and CEAC-determined causes of hospitalisation and deaths and hospitalisation (combined). However, there is potential bias, as adjudicators may base their decisions on information reported by the investigator, which cannot be independently verified, and three of the CEAC members were involved in algorithm development. Notably, there was a higher rate of disagreement between CEAC adjudicators (30% disagreement rate between the first and second adjudicator; perhaps reflecting the absence of a gold-standard definition for respiratory-related hospitalisations), than between CEAC adjudicators and investigators (6% discordance). Although the disagreement rate between the adjudicators may be viewed as a limitation, one could argue that these findings suggest that if sites are well selected, investigators can accurately categorise hospitalisations without the need for central adjudication. While investigators may correctly classify events in most cases, these data show that their diagnosis can be corroborated by respiratory experts who are unfamiliar with the case, using a standardised process with predefined criteria. Furthermore, the high rate of agreement we report may reflect the experience of the ISABELA investigators. These findings may not be replicated in other clinical trials, as each differs with regards to the robustness of their data, and decisions made by site investigators are subject to many variables, including the framework within which they work and the level of support they receive from contract research organisations and sponsors. Central adjudication may help classify trial outcomes where

there is variation or uncertainty in investigator-determined events and provide additional transparency. The algorithm defines a prescribed method for classifying outcomes, which can be used to compare data from future trials. In addition, the algorithm informs which clinical data are needed to retrospectively classify events and could therefore be programmed into data capture systems before trial onset. The algorithm could also be used by site investigators to increase homogeneity and efficacy in the reporting of events.

The ISABELA studies enrolled 1306 patients, comprising the largest IPF population studied to date, and generated longer-term data than previous IPF trials. Although registry data on outcomes following hospitalisation are available [2, 65], such data have not been systematically reported in the literature for previous trials. The ISABELA programme provides a sentinel cohort for the algorithm; our results indicate that the algorithm works well. Due to the early termination of the ISABELA studies, it was not possible to follow patients to determine the prognostic implications of differentiating the type of respiratory-related hospitalisation, but this could be investigated in future prospective IPF trials.

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Details of the ISABELA trials have previously been reported. Study protocols were approved by the independent ethics committee/institutional review board for each site or country, as applicable and all patients provided written informed consent.

Author contributions: P. Ford, K.K. Brown, N. Hirani, J. Behr and R.J. Kaner developed the original draft of the algorithm. P. Ford, M. Kreuter, K.K. Brown, W.A. Wuyts, M. Wijsenbeek, N. Hirani, J. Behr, R.J. Kaner and T.M. Maher reviewed and provided feedback on multiple iterations of the algorithm. P. Ford, M. Kreuter, K.K. Brown, W.A. Wuyts, M. Wijsenbeek and T.M. Maher were involved with the study design of the ISABELA trials. D. Israël-Biet, R. Hubbard, S.D. Nathan, H. Nunes, P. Spagnolo and R.J. Kaner were members of the CEAC for the ISABELA studies, which was co-chaired by N. Hirani and J. Behr. N. Prasad, I. Seghers and N. Verbruggen were responsible for setting up the electronic adjudication system and reviewed the adjudicated data on an ongoing basis throughout the ISABELA studies. B. Penninckx, N. Prasad, I. Seghers and N. Verbruggen contributed to the analysis and interpretation of the CEAC/study investigator concordance data. All authors critically reviewed drafts of this manuscript and approved the final version for submission.

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