Lack of diversity in antifibrotic trials for pulmonary fibrosis: a systematic review

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Shareable abstract (@ERSpublications)
Clinical trials of antifibrotic therapy for people with idiopathic pulmonary fibrosis frequently lack diversity; most participants are male and White with fewer than 1% Black participants. There is urgent need to validate therapeutics in diverse cohorts. https://bit.ly/3Pa6bjX

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Abstract

Introduction Social determinants of health (SDH), including age, sex, ethnicity, socioeconomic status and rurality, influence health outcomes. Clinical trials investigating antifibrotic agents for people with idiopathic pulmonary fibrosis (IPF) have been conducted in predominantly White and male populations; it is unclear whether other SDH have been considered. This study aimed to investigate active consideration and reporting of SDH in clinical trials of antifibrotic agents for people with IPF.

Methods Three registries (ClinicalTrials.gov, ANZCTR and International Standard Randomised Controlled Trial Number (ISRCTN)) plus CENTRAL (Cochrane Central Register of Controlled Trials) were searched for clinical trials investigating antifibrotic agents for people with IPF or various progressive fibrotic ILD variants registered from 1 January 2000 until 3 September 2023. Data were extracted regarding trial phase/status, recruitment strategies and eligibility criteria. If trial results were available, SDH data from demographics and subgroup analyses were extracted.

Results Of 313 records identified, 70 trials were included. The majority of trials were phase II or III (77%), 56% were completed and 61% had reported results that included eight terminated trials. All 70 trials specified age and sex, but not other SDH, within their eligibility criteria. Of 43 trials reporting results, all reported age and sex and 40 (95%) reported ethnicity. 10 387 participants were described (74% male, 77% White, 16% Asian and <1% Black). Descriptors for ethnicity varied considerably. Five trials (12%) included only White participants and three (7%) included only Asian participants. No other SDH were reported.

Conclusions SDH beyond age, sex and ethnicity were neither considered nor reported in antifibrotic IPF trials. Trial populations were predominantly male and White. There is a need to actively consider SDH to ensure diverse and representative clinical trial populations.

Introduction

Interstitial lung disease (ILD) is an umbrella term used to describe a group of heterogenous lung diseases characterised by progressive fibrosis of the lung parenchyma [1]. The aetiology of ILD can be categorised broadly into known and unknown causes, with known causes related to environmental exposures, such as asbestos or silica dust, or systemic auto-immune diseases, such as rheumatoid arthritis or scleroderma. ILD with unknown causes remains the most common variant, of which idiopathic pulmonary fibrosis (IPF) is the most common type [2]. Antifibrotic agents aim to slow the progression of pulmonary fibrosis and are currently the most effective treatment options available to people with IPF. Currently, there are two approved antifibrotic medications, namely nintedanib and pirfenidone [3].

The prevalence and severity of IPF, like other chronic respiratory diseases, is not experienced evenly across society [4–7]. Social determinants of health (SDH) include, but are not limited to, sex and gender (related but distinct biological and social constructs, respectively [8]), race and ethnicity (related but distinct social constructs describing perceived common physical traits or shared cultural expressions, respectively [9]),

place of residence, and socioeconomic status [10]. SDH impact how people access and experience healthcare, resulting in inequity in health outcomes known as the "social gradient of health" [10]. The extent to which health interventions are designed for, and validated in, diverse populations can impact their accessibility, acceptability and effectiveness in frequently disadvantaged groups [11]. Failure to do so can inadvertently result in development of interventions that broaden healthcare inequity gaps [11].

Population modelling of IPF epidemiology indicates that the prevalence of IPF is generally greatest amongst men and people who are White [12, 13]. Nevertheless, an audit of over 250 000 decedents with IPF in the USA between 1989 and 2007 revealed that 47% were women [6] and the greatest estimated prevalence of IPF globally has been reported in South Korea [14]. Although the typical IPF patient may be White and male, these figures highlight the impact of IPF expands beyond this demographic and reinforce the need to consider the role of sex and ethnicity when validating new treatments to ensure they are safe and effective for all people living with IPF.

In addition to biological variables, there is substantial evidence of worse health outcomes for people with IPF who are socioeconomically disadvantaged [15] or who reside in rural areas [5]. The impact of these social factors on acceptability and effectiveness of new treatments cannot be disregarded. A recent systematic review and meta-analysis of randomised controlled trials and registry studies targeting IPF has shown that racial and gender inequities exist, with women and people who are not White underrepresented in research studies [16]. Whether other SDH (such as place of residence and socioeconomic status) are reported in IPF research has not been thoroughly examined [17], nor is it clear whether there is proactive consideration of SDH at the trial design stage that may promote or hinder diversity. This issue of under-representation among clinical trial populations is not unique to IPF, being recognised in clinical research in other areas including critical care, chronic respiratory disease, and oncology [18–20].

This study therefore aimed to determine to what extent, if any, were interventional trials investigating antifibrotic agents for people with IPF 1) actively considering recruitment of people from diverse SDH groups, 2) recruiting participant cohorts which are representative of the relevant population, 3) describing SDH when reporting study results and 4) achieving equitable participation and health outcomes across SDH.

Methods

The protocol for this systematic review was developed *a priori* in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) checklist [21] and registered with Open Science Framework (https://doi.org/10.17605/OSF.IO/2SG7J) using the generalised systematic review registration form (https://osf.io/by27q/). The results are presented here in accordance with the PRISMA checklist.

Search strategy and study selection

An adapted systematic review process was adopted, with a comprehensive search conducted of three clinical trial registry databases, as follows: Australian New Zealand Clinical Trials Registry (ANZCTR), ClinicalTrials.Gov (USA) and International Standard Randomised Controlled Trial Number (ISRCTN) (UK). The search aimed to identify all interventional clinical trials investigating antifibrotic agents in adults with IPF or various progressive fibrotic ILD variants registered between 1 January 2000 and 3 September 2023. This adapted methodology is in alignment with previous systematic reviews of clinical trial registries [22, 23].

Search terms were restricted by functionality of clinical trial registries that do not uniformly accept advanced search functions such as Boolean operators or MeSH (Medical Subject Headings) terms. An additional search of the Cochrane Central Register of Controlled Trials (CENTRAL), which enabled more robust advanced search functions, was conducted on 3 September 2023 to supplement results obtained directly from the three targeted registries.

Our search strategy yielded both clinical trial registry records and publications, including protocol papers, primary results and secondary analyses. All publications were screened and if deemed to describe a potentially eligible study, the full-text was manually searched to identify any associated clinical trial registry record which was then manually added if not already captured in the search results. Where a clinical trial registry record in one of the included registries was not identified, the study described in the publication was not eligible for inclusion. Any publications associated with included studies were retained for data extraction; however, the total number of associated publications was not formally counted. This process is outlined in figure 1.

Subject headings and keywords for illness related terms included "interstitial lung disease", "pulmonary fibrosis", "idiopathic pulmonary fibrosis", or related MeSH terms where allowed. Subject headings and

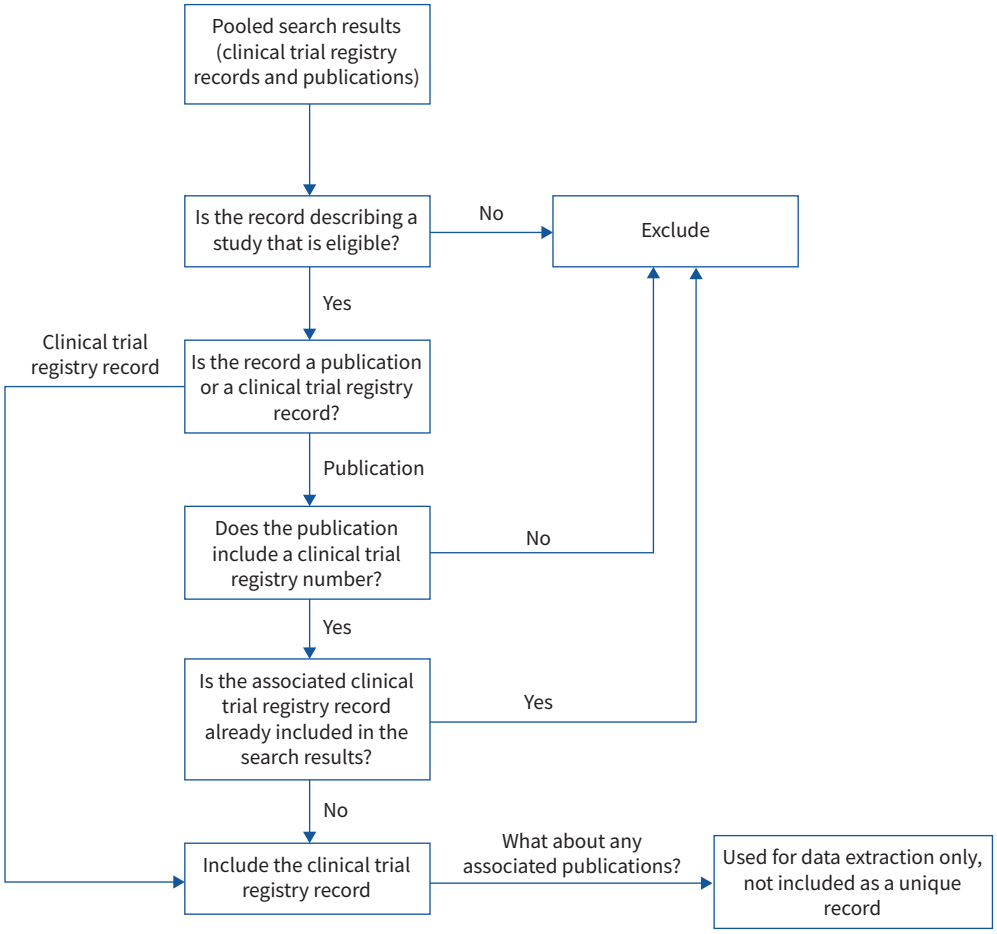

FIGURE 1 Search approach.

keywords for intervention related terms were excluded from registry searches as preliminary searches indicated that these terms were not reliably used in registry records. Intervention related terms in the supplemental CENTRAL search included "interstitial lung disease" and "anti-fibrotic agents" related MeSH terms. The full search approach is detailed in supplementary table S1.

Studies were included in our systematic review if they were registered on any of the three included registry databases between 1 January 2000 and 3 September 2023 and investigated any antifibrotic agent given *via* any delivery route for treatment of pulmonary fibrosis in adults. Studies which included people with IPF only, or various progressive fibrotic ILD variants, were eligible for inclusion. However, studies which only enrolled a single non-IPF variant of ILD (*e.g.*, exclusively scleroderma or exclusively silicosis) were not eligible for inclusion. This approach was adopted to ensure population homogeneity and allow comparison between trial populations and the known epidemiology for ILD in the community. Whilst ILD epidemiology in general remains poorly defined, there is considerable variation in epidemiology amongst different subtypes of ILD [24]. Any interventional study design, including randomised parallel-arm, randomised crossover and single-arm trials were eligible. Any comparator was permitted, including no comparator. Studies could be of any trial phase and any completion status, including ongoing or terminated trials.

Data from open-label extension studies were eligible for inclusion. Although extension studies inherently double-count recruitment of previous research participants, it was considered that the new and potentially clinically relevant data generated in extension studies warranted examination of the cohort demographics.

Outcomes

The primary outcome of interest for this systematic review was active consideration and reporting of SDH, including age, sex or gender, race or ethnicity, place of residence, and socioeconomic status as indicated by education, occupation or income, within trial populations. Active consideration was indicated by

1) description of any SDH of interest in eligibility criteria or recruitment strategies, and 2) description of SDH in actual participant demographics.

Secondary outcomes of interest were diversity of trial populations as indicated by reported demographic characteristics where available, any trial participation outcomes (*e.g.*, completion, withdrawal or loss to follow up) and health outcomes (*e.g.*, effectiveness or adverse events) stratified by SDH.

Data extraction

Two review authors (A.P. and E.C.) independently screened abstracts and full-text articles to determine eligibility for inclusion with disagreements resolved by discussion. Where consensus could not be met, a third reviewer (N.S.) resolved outstanding conflicts. Outcome data were extracted independently by two authors (A.P. and E.C.) for all included studies from the source. Sources included clinical trial registry records as well as any associated documents where available, including full protocols, published protocol papers, published results papers and other miscellaneous sources including sponsor reports or synopses (figure 1).

Data synthesis

Data were synthesised and are presented descriptively as three groups, as follows:

1) *Analysis 1*: an overall analysis including all registered trials with a focus on prospective consideration of SDH in eligibility criteria and stated recruitment strategies, planned demographics reporting, and planned subgroup analyses related to SDH.
2) *Analysis 2*: a subgroup analysis of all trials with publicly available results with a focus on actual reporting of SDH in participant demographics and any relevant subgroup analyses. Trials with publicly available results included completed trials, interim analyses or terminated trials and were sourced from articles published in peer-reviewed journals, results published directly to the clinical trial registry or results disseminated in publicly available sponsor documents.
3) *Analysis 3*: an exploratory subgroup of trials with publicly available results, but restricted to those which have been considered landmark trials in the development of pirfenidone and/or nintedanib [25]. These will be analysed and presented separately to provide a concise overview of the demographics which have contributed to the evidence base for the two currently approved antifibrotic agents.

Each of the four aims stated in the introduction were considered within each analysis.

Results

Search results

A total of 313 records were identified from the search after removal of duplicates. An additional eight records were identified during the screening process with 185 records in total selected for full-text retrieval, of which 70 records describing 70 registered trials were included in this review (figure 2 and supplementary table S2). Reasons for exclusion at full-text screening were predominantly on the basis of wrong study population; six studies were excluded on the basis of wrong intervention and, of these, four investigated sildenafil and two were nondrug interventions. Of these 70 registered trials, 24 had publicly available protocol documents and 43 had results available in the form of peer-reviewed publications, registry updates or sponsor synopses.

Analysis 1: All registered trials (n=70)

Characteristics of all included registered trials

Of the 70 included registered trials, 39 (55.7%) had been completed, 20 (28.6%) were ongoing at various stages of recruitment and 11 (15.7%) had been terminated (table 1). The most common reason for termination was an unfavourable benefit–risk profile (n=5). The majority of trials were phase II (n=35, 47.4%) or III (n=20, 27.1%) and most frequently utilised a parallel assignment study design (n=55, 78.6%). All but three trials were sponsored by pharmaceutical companies and the majority (n=59, 84.3%) were multi-site. Most planned to include study sites in one or more high-income (n=62, 88.6%) or upper middle-income (n=34, 48.6%) countries. Only four trials (5.7%) planned to include study sites in one or more lower middle-income countries and none included low-income countries.

Over half (n=39, 55.7%) of the registered trials were investigating novel antifibrotic agents, none of which have since progressed to the market for IPF. The remaining trials were investigating nintedanib or pirfenidone, either alone or in combination with each other or another novel agent.

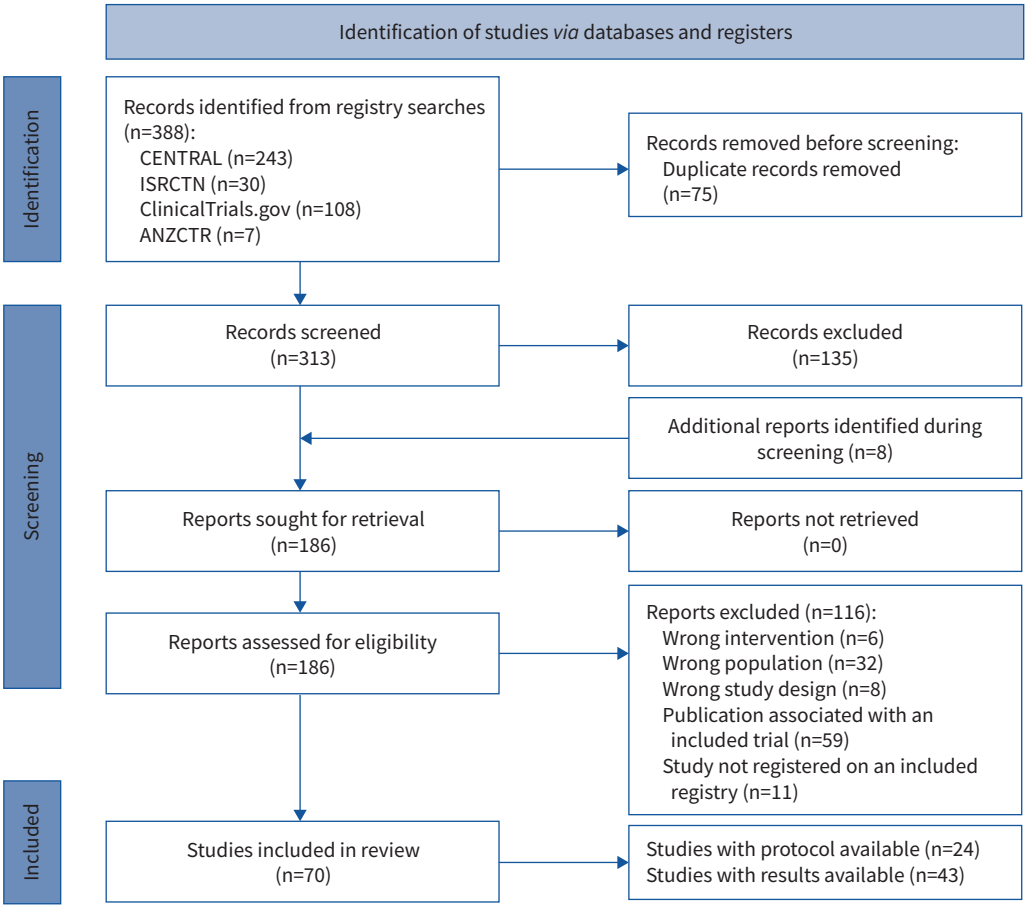

FIGURE 2 Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram. ANZCTR: Australian New Zealand Clinical Trials Registry; CENTRAL: Cochrane Central Register of Controlled Trials; ISRCTN: International Standard Randomised Controlled Trial Number.

Prospective consideration of SDH: eligibility criteria, recruitment strategies and proposed subgroup analyses

Of the 70 registered trials, all included some description of age and sex or gender within the eligibility criteria (table 2). All trials specified a minimum age and 32 (45.7%) specified a maximum age. The most common minimum age was 40 (n=54, 77.1%) and the most common maximum age was 80 (n=16, 22.9%). Two trials specified different minimum ages for men and women; one specified over 50 for men and over 55 for women, whilst another specified women must be over 40 whilst men only needed to have completed family planning with no minimum age stated. Sex and gender were broadly mentioned specifying that "all sexes were eligible"; however, 37 trials (52.6%) excluded women who were pregnant, breastfeeding or of childbearing potential. No trials described eligibility criteria for intersex, nonbinary or other gender-diverse people.

None of the registered trials specified race or ethnicity within the eligibility criteria; however, four trials (5.7%) specified Chinese or Japanese cohorts within the trial title, though it was unclear if this referred to nationality or ethnicity. No eligibility criteria or recruitment strategies relating to indicators of socioeconomic status (education, occupation or income) or place of residence were described; however, one trial excluded participants who were unable to attend study visits in person.

The majority of trials (n=58, 80.0%) provided no details regarding recruitment strategies in the registry or any associated protocol documents. Seven trials (10.0%) were extension trials and sourced participants from earlier studies, five (n=7.1%) specified the clinical sites where recruitment would take place and two (2.9%) had public-facing websites with information regarding the trial. No specific strategies to promote diversity were described in any trial.

TABLE 1 Characteristics of included registered trials

Trial characteristics	All registered trials (n=70)		Trials with results (n=43)	
	n	%	n	%
Study status				
Completed	39	55.7	35	81.4
Ongoing	20	28.6	0	0.0
Terminated	11	15.7	8	18.6
Trial phase[#]				
I	13	17.1	6	14.0
II	35	47.4	21	48.8
III	20	27.1	13	30.2
IV	4	5.7	4	9.3
Study design				
Parallel assignment	55	78.6	34	79.1
Crossover assignment	1	1.4	0	0.0
Sequential assignment	3	4.3	0	0.0
Single arm	11	15.7	9	20.9
Intervention				
Pirfenidone[¶]	14	20.0	12	27.9
Nintedanib[¶]	12	17.1	10	23.3
Nintedanib+pirfenidone	3	4.3	3	7.0
Pirfenidone or nintedanib+other novel agent	2	2.9	1	2.3
Other novel agents[+]	39	55.8	17	39.5
Trial sponsor				
Pharmaceutical company	67	95.7	43	100.0
University or hospital	3	4.3	0	0.0
Study sites by GNI income thresholds[#§]				
High	62	88.6	42	97.7
Upper middle	34	48.6	11	25.6
Lower middle	4	5.7	3	7.0
Low	0	0.0	0	0.0
Year registered				
2000–2004	1	1.4	1	2.3
2005–2009	4	5.7	4	9.3
2010–2014	15	21.4	14	32.6
2015–2019	27	38.6	23	53.5
2020 onwards[f]	23	32.9	1	2.3

[#]: Trials can be included in more than one category. [¶]: Includes novel formulations. [+]: No more than three trials conducted on any given novel agent. Some studies conducted post-approval of nintedanib and pirfenidone permitted stable background therapy with these agents. [§]: Gross national income (GNI), count of studies with at least one site in a given income threshold. [f]: Fewer years compared to other groupings.

15 (21.4%) trials indicated that they would collect data on age and 14 (20.0%) indicated that they would collect data on race or ethnicity; however, the majority of trials (n=54, 77.1%) made no specific mention of which demographic characteristics would be collected or reported. The majority of trials (n=58, 82.9%) indicated no planned subgroup analyses on the basis of SDH. Amongst the remaining trials, nine (12.9%) described subgroup or adjusted analyses based on age, eight (11.4%) on the basis of sex/gender, two (2.9%) on the basis of race/ethnicity and three (4.3%) on the basis of region of recruitment. One trial (1.4%) had subgroup analysis plans that had been redacted from the available protocol and one (1.4%) stated only "various subgroups of interest".

Analysis 2: trials with results (n=43)

Characteristics of included trials with results available

Of the 43 trials with publicly available results, 35 (81.4%) had been completed and eight (18.6%) had been terminated (table 1). Reasons for termination included unfavourable benefit–risk profile (n=5), sponsor decisions or change in business objectives (n=2) and sufficient information gathered from prior studies (n=1). The majority of trials were phase II (n=21, 48.8%) or III (n=13, 30.2%) and most frequently utilised a parallel assignment study design (n=34, 79.1%). All trials were sponsored by pharmaceutical companies.

TABLE 2 Prospective consideration and retrospective reporting of social determinants of health (SDH)

Social determinant	All registered trials (n=70) (prospective strategies)			Trials with results (n=43) (retrospective reporting)		
	n	%	Detail	n	%	Detail
Sex or gender	70	100.0	All specified all sexes eligible 53% excluded WCBP	43	100.0	Data available for 10 387 participants Male (n=7730, 74.4%)
Age	70	100.0	Minimum age 18 (n=10) 21 (n=1) 40 (n=54) 45 (n=2) 50 (n=2) 55 (n=1) Maximum age 55 (n=1) 75 (n=2) 79 (n=1) 80 (n=16) 84 (n=1) 85 (n=10) 90 (n=1)	43	100.0	Mean age: 68 years (SD 7.49)
Race or ethnicity	0	0.0	No trials prospectively reported specific strategies for recruitment in relation to race or ethnicity Four refer to Chinese or Japanese cohorts within title but did not specify if this refers to nationality or ethnicity	40	95.2	Retrospective data was available for 9617 participants: White (n=7413, 77.1%) Asian (n=1559, 16.2%) Black (n=39, 0.4%) Data available for 3313 participants: Hispanic (n=411, 12.4%)
Education	0	0.0	NA	0	0.0	NA
Occupation	0	0.0	NA	0	0.0	NA
Income	0	0.0	NA	0	0.0	NA
Place of residence	0	0.0	One excluded people who could not attend in-person visits	0	0.0	NA

NA: not applicable; WCBP: women of childbearing potential.

Nearly all trials with results (n=42, 97.7%) included study sites in at least one high-income country, a quarter (n=11, 25.6%) included study sites in at least one upper middle-income country and only three (7.0%) included study sites in at least one lower middle-income country. No study sites were located in low-income countries.

The majority (n= 26, 60.5%) of trials were investigations of nintedanib or pirfenidone, either alone or in combination with each other or another novel agent. The remaining trials were investigating novel antifibrotic agents, none of which have since progressed to market for this indication.

Retrospective reporting of SDH: participant demographics and actual subgroup analyses

Among the 43 trials with results, there was a total of 10 387 participants included. All results included some description of age and sex or gender within the reported participant demographics (table 2). The mean age of participants was 68 years (SD 7.49) and the majority of participants were male (n=7730, 74.4%), with a median of 75.7% male participants per study (interquartile range 71.3–81.8%). Four trials (9%) included fewer than 10% female participants.

Data on race or ethnicity were available for 40 trials (95.2%) with a total of 9617 participants included. Categories and descriptors used for race and ethnicity varied considerably across studies and, in some instances, only provided data on the majority category, which was typically White. Descriptions of race and ethnicity data provided directly in registry records were generally more detailed than those described in associated publications. Descriptors which were broadly aligned with the broad categories of “White”, “Asian” and “Black” were consolidated for this analysis similar to previous analyses of ethnicity data [9]; however, not all studies provided data on all three categories. The majority of participants were described

as White (n=7413, 77.1%), with the next more frequent category being Asian (n=1559, 16.2%). Fewer than 1% of participants were described as Black or African American (n=39, 0.4%). Five trials (12%) included only White participants and three (7%) included only Asian participants. No trials included only Black participants.

The remaining 6.3% of trial participants for which there were race or ethnicity data available could not be easily consolidated; this number includes participants whose race or ethnicity was unknown or missing. Of note, studies conducted in France explicitly prohibited collection and reporting of race or ethnicity data, which in some multinational studies contributed to unknown or missing data.

Of the 40 trials with race or ethnicity data, 16 studies with 3313 participants primarily based in the United States additionally provided a description of Hispanic or non-Hispanic participants. Amongst these 16 studies, there was a mean of 12.4% Hispanic participants included (n=411). Data on Indigenous persons was limited with a total of 40 participants overall being described as American Indian, Alaskan Native, Native Hawaiian or Pacific Islander. No other Indigenous groups were described.

No descriptions of place of residence or any indicators of socioeconomic status (education, occupation or income) were reported.

In the reported results, most trials (n=36, 83.7%) reported no subgroup analyses on the basis of SDH. Two reports from four studies (9.3%) all investigating nintedanib, INPULSIS I and II [26], INBUILD and INBUILD-ON [27], reported subgroup analyses of Asian participants in secondary publications. In these subgroup analyses there was a noted increase in frequency of adverse events, namely diarrhoea and abnormal hepatic function, amongst Asian participants compared to overall trial populations [26, 27].

One study reported subgroup analyses for age (<65 *versus* ⩾65 years) and sex/gender (male *versus* female) [28]. Beneficial treatment effect on mean change in forced vital capacity recorded in all groups, albeit a lower mean change in women and in people under 65 with the lower limits of the reported 95% confidence intervals approaching or crossing parity (women: 1.3–158.0 mL; men: 20.0–197.1 mL; <65: −50.3–140.1 m; ⩾65: 46.3–198.7 mL) [28].

One study described stratification of results by sex in the methods section of the results paper, although this analysis could not be identified in the results or supplementary data [29]. One reported results adjusted for age and gender but did not provide separate subgroup outcomes [30].

Notably, actual reported subgroup analyses had poor concordance with planned subgroup analyses described in protocol documents with six trials who had described planned SDH-based subgroup analyses reporting none and two who had not specified planned SDH-based subgroup analyses going on to report results that were adjusted or stratified for sex, age or ethnicity.

Analysis 3: landmark trials of pirfenidone and nintedanib (n=10)

11 trials with 5280 participants were included in the subgroup analysis of trials that have been considered landmark in the development and approval or pirfenidone and nintedanib (table 3) [25]. Of these, two were replicate trials (CAPACITY x2) and three were open-label extensions of earlier studies (TOMORROW open-label extension, the RECAP extension of CAPACITY and ASCEND, and the INBUILD-ON extension of INBUILD). Six investigated nintedanib (TOMORROW, TOMORROW extension, INPULSIS I and II, INBUILD and INBUILD-ON), five investigated pirfenidone (CAPACITY x2, ASCEND and RECAP) and one investigated combined therapy (INJOURNEY).

All 11 trials retrospectively reported sex or gender of participants with the majority being male (71.0%). 10 trials retrospectively reported race or ethnicity with a weighted average of 77.2% of participants described as White, 13.0% Asian and 1.7% Black. Notably, this includes trials which did not describe prospective plans regarding race or ethnicity. Only four trials, all investigating nintedanib, reported the proportion of participants that were Black; INPULSIS I was notable as having 14.2% Black participants whilst the other three, INPULSIS II, INBUILD and INBUILD-ON, had 1.5% or fewer. No landmark trials of pirfenidone reported any Black participants and only one (INJOURNEY – combined nintedanib and pirfenidone) reported the proportion of Asian participants, which was 3.8%.

Discussion

This systematic review of ongoing, terminated and completed registered clinical trials of antifibrotic agents for people with IPF found a lack of prospective consideration of SDH beyond age and sex or gender in

TABLE 3 Demographic reporting from landmark trials of pirfenidone and/or nintedanib

Trial name (year)	Trial ID	Phase	Treatment	Sample size	% Male	% White	% Asian	% Black	Notes
TOMORROW (2011)	NCT00514683	2	Nintedanib	428	74.8	79	21	–	
	NCT01170065	2	Nintedanib	198	71.2	–	–	–	Open label extension
CAPACITY (2011)	NCT00287729	3	Pirfenidone	344	71.8	98.8	–	–	Replicate trials
	NCT00287716	3	Pirfenidone	435	71.5	96.3	–	–	
ASCEND (2014)	NCT01366209	3	Pirfenidone	555	78.4	>90	–	–	
INPULSIS I (2014)	NCT01335464	3	Nintedanib	513	80.7	64.9	20.9	14.2	
INPULSIS II (2014)	NCT01335477	3	Nintedanib	548	77.9	50.2	39.2	0.2	
RECAP (2017)	NCT00662038	3	Pirfenidone	1058	74.7	95.2	–	–	Extension of ASCEND and CAPACITY
INJOURNEY (2018)	NCT02579603	4	Nintedanib Pirfenidone	104	82.7	96.2	3.8	–	
INBUILD (2019)	NCT02999178	3	Nintedanib	663	53.7	73.6	24.6	1.5	
INBUILD-ON	NCT03820726		Nintedanib	434	51.4	64.3	24.9	0.9	Extension of INBUILD
Total sample size				5280					
Weighted averages					**71.0**	**77.2**	**13.0**	**1.7**	

–: Not reported.

trial documents and limited retrospective reporting beyond age, sex or gender, and race or ethnicity in trial results. Where SDH were described, trials lacked diversity with the majority of participants being male and White.

Our findings are consistent with broader investigations of clinical research [16, 19, 20] that have found that women and people who are not White are frequently under-represented. Whilst it is well-recognised that IPF is more commonly reported amongst men and as such a higher proportion of men may be appropriate, the inclusion of adequate numbers of women in clinical research is essential to understand sex-based differences related to disease progression or treatment effects [31]. Our finding that 9% of trials with results included fewer than 10% female participants signals that under-representation of women is a significant issue. Importantly, our systematic review expands upon a previous meta-analysis which examined sex and ethnicity in published randomised controlled trials and registry studies of people with IPF [16] to capture all registered trials, including ongoing and terminated trials. This approach, which was not limited to trials that have published results, enabled a more expansive view of diversity (or lack of) within trial populations. Further, the subsequent publication of RECAP [32], INBUILD [33] and INBUILD-ON [34], which were not included in the earlier analysis but add considerable safety monitoring and effectiveness data for pirfenidone and nintedanib, respectively, remain predominantly White, showing a concerning lack of progress in racial diversity.

Descriptors used to capture race and ethnicity data remain a challenging topic as there is a need to balance standardised terms which facilitate transparent reporting and benchmarking against the reality that race and ethnicity are constantly evolving social constructs which cannot perfectly reflect all individuals unique identities [9]. There have been considerable efforts to develop and adopt standardised terms to guide research reporting, such as the National Institutes of Health defining six categories which broadly reflect the United States demographics [35]. Despite this, there remains a tendency for research to be collapsed into White *versus* "non-White" categories even when more detailed data have been collected [36]. In addition to stripping important nuance from data, this approach undermines the contribution of many research participants by centring whiteness as the default [36].

Although a previous study indicated under-representation of people who are not White in clinical trials and registry studies [16], our systematic review highlights the magnitude of this issue. The proportion of "non-White" participants in IPF antifibrotic clinical trials (which included over 10 000 research participants) largely comprised people who were Asian (n=1559, 16.2%), with only 39 (0.4%) people who were described as Black. This finding is further obscured by binary reporting that is limited to people who are White or "not White". It is highly concerning that IPF antifibrotic clinical trials were so exclusive and that so few Black people were included.

Furthermore, the extremely limited data from these trials on the safety and effectiveness of antifibrotic agents in people who are Black is a serious concern, which limits generalisability and transferability of

clinical findings. A recent audit of over 47 000 people with IPF in the United States highlighted that people who are Black were prescribed antifibrotic agents at half the rate of people who are White [7]. In addition to describing social factors, such as economic hardship and systemic racism, that may limit the ability of people who are Black to obtain an antifibrotic prescription, the authors of that study highlighted that clinicians may feel ill-equipped to manage IPF in patients who are Black due to limited experience and a limited evidence base, particularly given high rates of comorbid liver disease amongst this population and the known hepatotoxic effects of antifibrotic agents [7]. Although no subgroup analyses of Black trial populations were identified, when subgroup analyses were conducted with Asian populations, increased rates of hepatotoxic adverse events were identified [26, 27] indicating different risk profiles across ethnic groups. Further, without stratification of participants by both sex and ethnicity, it is impossible to know how many, if any, women who are Black or Asian have been enrolled in clinical trials. Given known differential mortality patterns across sex and ethnic groups within IPF, there is a need to better understand how these interactive factors may impact safety and effectiveness of potential therapeutics [6].

Prospective consideration of SDH was frequently superficial and lacked descriptions of recruitment strategies that may promote inclusivity and diversity in trial populations. Without proactive strategies (*e.g.*, inclusion of regional recruitment sites that serve lower socioeconomic populations or remote trial participation), trials are unlikely to recruit under-represented populations [11, 37]. Though all studies were open to recruitment of both men and women, women of childbearing potential were excluded or only conditionally eligible in over half of trials. This is not unique to IPF research and is routinely utilised in many early-phase pharmacological trials out of safety concerns for fetal health; however, there is a need to balance these concerns with respect for the autonomy of women [38]. One trial included in this review excluded women under 40 but only required men to have completed their family planning which suggests a distrust of women to prevent pregnancy, as well as assuming all women are heterosexual and sexually active.

Our systematic review identified a complete lack of consideration or reporting of any other SDH, including place of residence and indicators of socioeconomic status. Socioeconomic disadvantage and living in a rural area have each been shown to limit inclusion in clinical research more broadly [39, 40]. Though these social factors are not as immediately compelling as the biologically plausible factors of sex and ethnicity when considering the safety and effectiveness of new therapeutics, they play a complex role in health outcomes and should not be disregarded when determining the acceptability and effectiveness of any new treatment [41]. Transparency in reporting of socioeconomic status and place of residence can also help to disentangle differential health outcomes that are due to intrinsic biological differences from those that are due to sociopolitical barriers including discrimination and segregation which are often confounding factors [17].

Strengths and limitations

This systematic review utilised an adapted systematic review approach which was informed by, and expands upon, methods used in previous reviews [22, 23] (focusing on identifying registered trials and then extracting data from associated publications) to examine not only how SDH are reported in clinical trial outcomes, but also to determine whether any pro-active consideration is given to these factors in the design and conduct of clinical research. It is possible that recruitment strategies to promote diversity were considered and implemented in the included trials, however there is a notable lack of transparency in these approaches. Similarly, it is possible that additional reporting of SDH and, particularly, subgroup analyses of safety or effectiveness by SDH, have been conducted and not reported.

It should also be noted that this study was limited to three major trial registries based in English-speaking countries. This was a pragmatic decision to avoid translation barriers and although the included registries do often include studies conducted outside of the United States, Europe, Australia and New Zealand, it is possible that an expanded search of other trial registries may yield more diverse results.

It is important to note that “sex” and “gender” are distinct but related terms describing biological and socially constructed characteristics, respectively. Similarly, “race” and “ethnicity” are distinct but related terms describing common physical traits and shared cultural expressions or identities. For both sex/gender and race/ethnicity, there is a lack of clear distinction and transparency between how these constructs have been collected and reported in the literature with the terms frequently used interchangeably. This limitation is symptomatic of broader lack of detailed and transparent reporting in clinical research.

Conclusions

Consideration and reporting of SDH beyond age, sex or gender, and race or ethnicity were absent. When trial populations were described, they were predominantly male and White. This trend was also notable in the subset of trials which have contributed to the marketing approval of pirfenidone and nintedanib which

highlights a concerning lack of diversity in the evidence base for the two currently available antifibrotic agents. There is an urgent need to actively consider SDH to ensure diverse and representative clinical trial populations.

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