Identifying outcome domains to establish a core outcome set for progressive pulmonary fibrosis: a scoping review

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Shareable abstract (@ERSpublications)
This scoping review identified 84 outcome domains described in IPF/PPF research papers covering qualitative and quantitative methodologies. This list will form a basis for the further development of a core outcome set for people living with PPF/IPF. https://bit.ly/4fyGbun

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Abstract

Introduction People with idiopathic pulmonary fibrosis (IPF) and other forms of progressive pulmonary fibrosis (PPF) have a high symptom burden and a poor health-related quality of life (HRQoL). Despite efforts to offer specialised treatment, clinical care for these patients remains suboptimal and several nonmedical needs remain unaddressed. Developing a core outcome set (COS) can help to identify a minimum set of agreed-upon outcomes that should be measured and acted-upon in clinical care.

Aim As a first step towards developing a COS for IPF/PPF, we aimed to identify outcome domains investigated in IPF/PPF research.

Methods Conducted within the COCOS-IPF (Co-designing a Core Outcome Set for and with patients with IPF) project, this scoping review follows Joanna Briggs Institute methodology and PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines to search PubMed, Embase and Web of Science for quantitative, qualitative and mixed-methods papers. We extracted each paper's outcomes verbatim and classified them using the COMET (Core Outcome Measures in Effectiveness Trials) taxonomy. Then, the research team structured outcomes or concepts with similar meanings inductively into outcome domains.

Results We included 428 papers, extracting 1685 outcomes. Most outcomes (n=1340) were identified in quantitative sources, which we could classify in 64 outcome domains, with the main domains being "all-cause survival" (n=237), "lung function" (n=164) and "exercise capacity" (n=99). Qualitative sources identified 51 outcome domains, with the most frequent being "capability to do activities you enjoy" (n=31), "anxiety, worry and fear" (n=26) and "dealing with disease progression" (n=25).

Conclusions The identified outcomes, spanning diverse domains, highlight the complexity of patient experiences and can form the basis to develop a COS for IPF/PPF clinical care, as well as future research.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a rare disease defined by an ultimately progressive and irreversible development of pulmonary fibrosis. It has a poor prognosis, with a median survival of between 3 and

5 years after diagnosis [1]. Recently, fibrosing interstitial lung diseases (ILDs) with a progressive phenotype have been classified as progressive pulmonary fibrosis (PPF) [2]. Although evidence is still limited, disease progression might lead to a similar disease trajectory and similar treatment needs as IPF [3]. Patients suffering from worsening lung fibrosis experience a high symptom burden, including breathlessness, cough and fatigue, as well as a significantly impaired health-related quality of life (HRQoL) [4–6].

Due to the complexity of IPF and other forms of PPF, which are difficult to diagnose and require specialised treatment, patient care is often centralised in centres of expertise. Recent research has shown that these centres have implemented various care models and components of care to best support patients and their caregivers and to improve their outcomes [7, 8]. For instance, considerable improvements in diagnostic and pharmacological practices have been made by establishing multidisciplinary care teams and standardised medical and pharmacological follow-up. In addition, several international evidence-based guidelines for diagnosis and treatment have been published recommending how to provide the highest quality of care for patients with IPF and PPF [1, 9]. However, although a retrospective study showed that bundling these recommendations improved outcomes such as transplant-free survival, these recommendations mainly target the medical and pharmacological dimension of care [10]. Improvements in person-centred and integrated care that also target psychosocial and palliative needs are only slowly receiving attention, despite the high need for support for the nonmedical aspects of these serious diseases, as was also highlighted in the European IPF patient charter [11] and other publications [12–14]. Additionally, there is heterogeneity in patient care across European countries, as shown in a benchmarking report of the European Idiopathic Pulmonary Fibrosis and Related Disorders Federation [15]. Hence, despite best intentions and efforts to address structures and processes of care, there remain gaps and variations in the care of patients with PPF and IPF that may heavily impact the quality of care.

As a first step toward standardisation, improvements and benchmarking in patient care and value, it is now widely accepted to measure outcomes that truly matter to patients [16]. Core outcome sets (COSs) are increasingly being developed to identify essential outcomes to measure and address in research and clinical care *via* consensus between stakeholder groups [16, 17]. In particular, the development and use of COSs in clinical trials are receiving growing interest, with several initiatives offering methodological guidance on how to develop these COSs [17–19]. Saketkoo *et al.* [20], for instance, developed a COS that can be used as end-points in randomised controlled trials in IPF and connective tissue disease (CTD)-related ILDs. Although it is recognised that a COS could also be relevant to provide high-quality person-centred care, the context of clinical care is often not considered during the COS development process. Currently, a COS for IPF and PPF clinical care is not available and it remains unclear which person-relevant outcomes need to be addressed to improve the quality of care.

This scoping review was conducted to identify outcome domains considered in both published quantitative and qualitative research on IPF/PPF. It represents a first critical step towards developing a COS for use in IPF/PPF related clinical care [17].

Methods

This scoping review was systematically conducted according to the methodological guidance of the Joanna Briggs Institute and reported using the PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) checklist [21, 22].

Search string

A search string was developed by the research team, consisting of ILD experts, psychologists, social scientists and patient representatives, with the assistance of an experienced information specialist at the KU Leuven. It comprises search terms pertaining to the health condition (*i.e.*, IPF and PPF) and to research methods (*e.g.*, survey and interview) as main concepts. The search string was first developed for use in the PubMed/Medline database and was then adapted for use in the Embase and Web of Science Core Collection databases. We retrieved records published in the last 10 years, both for feasibility reasons and to reflect changes in care practices following the availability of antifibrotic drugs (see appendix 1 for the electronic source search strategy and appendix 2 for the PubMed/Medline search string). The search was executed on 5 December 2022.

Inclusion and exclusion criteria

The following inclusion criteria were applied: 1) full-text papers; 2) written in English, French, Dutch, German and Turkish, since the team members were proficient in these languages; 3) published after 1 January 2012; 4) targeting patients older than 18 years with IPF or PPF (*i.e.*, chronic hypersensitivity

pneumonitis (HP), pulmonary sarcoidosis, connective tissue disease-associated ILDs (*e.g.* rheumatoid arthritis ILD, polymyositis ILD and systemic sclerosis ILD), (idiopathic) nonspecific interstitial pneumonia (NSIP), unclassifiable idiopathic interstitial pneumonia and diseases related to exposure (*e.g.* asbestosis and silicosis), provided that the population had a progressive fibrosing phenotype) [23]; and 5) investigating patient outcomes from a quantitative, mixed-methods or qualitative research source.

We excluded: 1) reviews, letters to editors, case reports, viewpoints, book chapters, conference abstracts, dissertations and patient summaries; 2) clinical drug phase I-III trials (as our focus was not on end-points); 3) papers targeting diseases other than IPF/PPF, besides frequently associated comorbidities; 4) papers focusing on the diagnostic phase exclusively or address the peri- or post-transplant period; 5) papers focusing solely on epidemiology, pathogenesis, gene profiling or biomarkers; and 6) papers that focused only on caregiver- or physician-related outcomes or on structures or processes of care.

Procedure

Records were retrieved from the databases on 5 December 2022 and imported into EndNote X9. De-duplication took place using the recommendations of Bramer *et al*. [24], after which remaining records were uploaded in the review management tool, Rayyan AI [25]. Researchers with multidisciplinary expertise and backgrounds (physicians, nurses, psychologists and a biomedical scientist), who received training to ensure a common understanding of the methodology, identified eligible papers through two screening phases. In the first phase, titles and abstracts were screened by pairs of researchers (*i.e.*, one physician and one social scientist) (pair 1: A.D. and N.T.; pair 2: S.S. and V.S.). Full-text articles of records deemed "potentially eligible" by at least one researcher in the first phase were assessed in a second screening phase. To facilitate the second screening phase, we developed a checklist with the inclusion and exclusion criteria, allowing the screeners to consider all inclusion criteria or to determine the reason for exclusion (see the checklist with the eligibility criteria in appendix 3). Prior to the second screening phase, we piloted this checklist with the eligibility criteria with 15 full texts and calculated the inter-rater agreement using the multi-rater kappa statistic described by Fleiss [26] and the AC1 statistic proposed by Gwet [27]. After obtaining substantial agreement between raters (*i.e.*, kappa>0.6 [28]), pairs of researchers assessed each full text using the piloted checklist and documented the reason for exclusion. In the absence of a final agreement between researchers, a third researcher entered the discussion until consensus was reached. Given the high number of included papers, the research team decided not to perform a "related article search" in PubMed/Medline, not to screen reference lists of included papers and not to contact authors for more information.

Data extraction

To facilitate data extraction and synthesis, we first separated the eligible papers based on design, *i.e.*, quantitative, qualitative and mixed-methods design. We extracted the following information using a piloted Excel data form: 1) study-specific information including year of publication, country(ies), study design, aim, setting, target population and patient involvement (*i.e.*, whether the authors actively worked together with patients or their representatives to develop the protocol and/or select the outcomes under investigation); and 2) verbatim data on outcomes (*e.g.*, forced vital capacity and walking distance), including definitions if provided, and corresponding outcome measures (*e.g.*, spirometry, 6-min walk test). For the data-extraction process, we used a broad definition of "outcomes" and considered them as the main concepts investigated in the included studies as stated in the papers' study aims. We refer to "QUAN outcomes" for outcomes yielded from quantitative papers, as well as quantitative outcomes from mixed-methods papers. "QUAL outcomes" refers to outcomes from qualitative papers and qualitative outcomes from mixed-methods papers. Since the aim of this scoping review was to provide an overview of the evidence and not to produce a critically appraised answer to a particular question, we did not perform a quality appraisal of the included papers [29].

All researchers were trained in the data-extraction process. As part of the training, we tested the data-extraction process with 10 papers to check the accuracy of data extraction between researchers. Data from the quantitative papers was then extracted by four researchers (A.D., V.S., N.T. and S.S.). Given the high number of included studies, this process was not executed by pairs of researchers independently. To ensure its accuracy, the quality of the data extraction was monitored by the team leader (A.D.) who randomly selected 10% of the papers with a quantitative research design, extracted the data independently and compared her results with the data documented in the data-extraction Excel form. The outcomes mentioned in qualitative studies and mixed-methods papers were extracted by one researcher (F.D.). with a background in psychology and reviewed by two other researchers (S.S. and N.S.). Processes (*e.g.*, medication and oxygen use) and structures (*e.g.*, availability of psychological care) of care were not extracted.

Data synthesis

Figure 1 provides a schematic overview of the data-synthesis process with examples.

First, all outcomes were extracted verbatim from the eligible papers, as described above. Once we retrieved all outcomes, we used the following steps to classify our data [17].

Step 1: We used the COMET (Core Outcome Measures in Effectiveness Trials) taxonomy to categorise the long list of outcomes retrieved verbatim [30]. The taxonomy proposes 38 outcome groups that refer to five areas (*i.e.*, mortality, physiological/clinical, life impact, resource use and adverse events). All outcomes that were extracted verbatim were categorised independently by two researchers with a multidisciplinary background. Differences in categorisation were discussed where needed with a third researcher. Given that certain outcomes could fall under multiple COMET categories, we assigned each outcome only to the category that best represents the outcome's content. These decisions were made in consensus between the researchers involved in this step. We classified "side-effects of medications" under the COMET category "adverse events". Given the wide range of pharmacological treatments currently offered for IPF and PPF, we did not extract individual side-effects (*e.g.* nausea or skin rash). Considering all possible side-effects from all pharmacological treatments would not fit the purpose of this review (which is to form the basis for a COS applicable to the care of the majority of people with IPF/PPF). Similarly, we did not classify the comorbidities into the respective COMET categories, but list them in a separate file (available upon request from the authors).

Step 2: We then removed true duplicate outcomes within each COMET category (*i.e.*, outcomes extracted with the same wording).

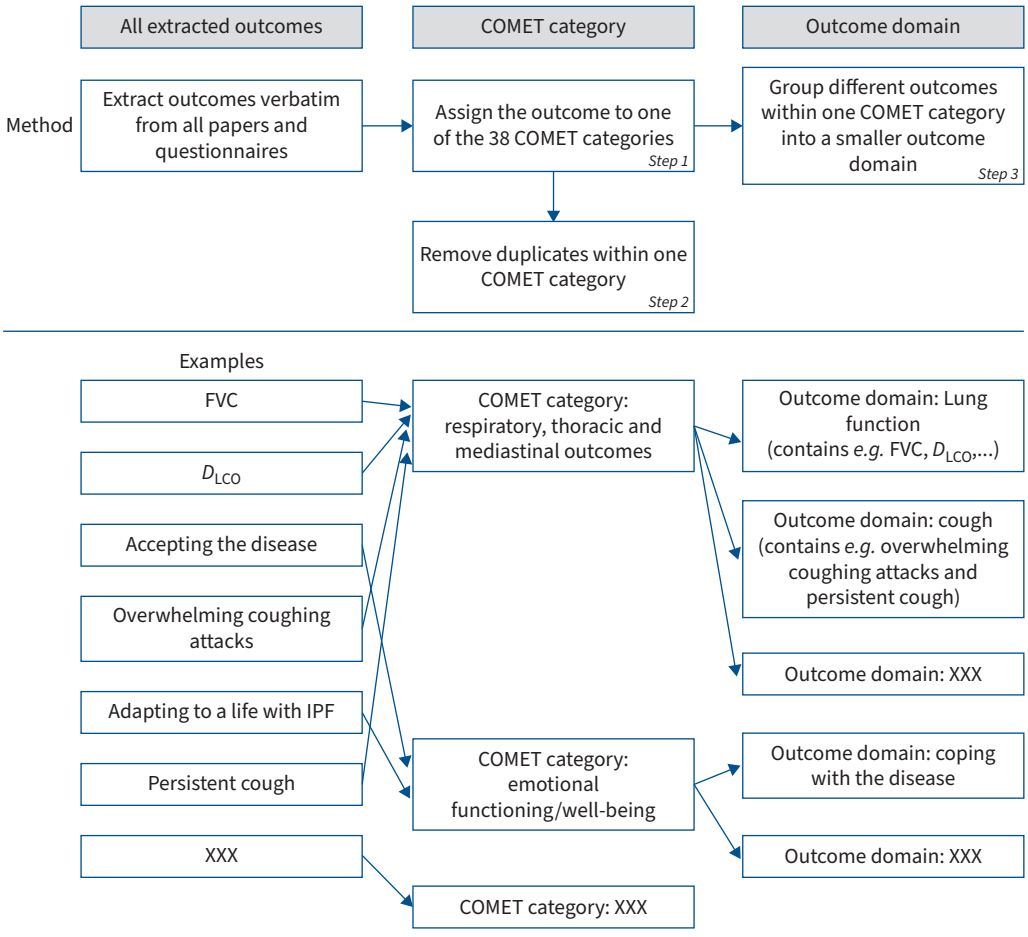

FIGURE 1 Schematic overview of the data synthesis process with examples. COMET: Core Outcome Measures in Effectiveness Trials; D_{LCO}: diffusing capacity of the lung for carbon monoxide; FVC: forced vital capacity; IPF: idiopathic pulmonary fibrosis; XXX: other outcomes, COMET category or outcome domain as emerging from the data.

Step 3: The outcomes categorised within the same COMET category were then inductively grouped/structured into so-called outcome domains by the research team as also recommended in the COMET handbook [17]. Outcome domains consist of groups of outcomes or concepts with similar meanings and are defined as "constructs which can be used to classify broad aspects of the effects of interventions" [17].

To double-check our classification and grouping of outcomes in outcome domains, the principal investigator (F.D.), who was not directly involved in the data extraction, reassessed the classification and grouping of the data.

This data analysis resulted in large datasets where individual outcomes were fitted within the COMET taxonomy and subsequently grouped into outcome domains.

"Forced vital capacity", for instance, was reported in several papers and first extracted verbatim. This outcome was subsequently classified under the COMET category "respiratory, thoracic and mediastinal outcomes". Next, "forced vital capacity", was grouped under the outcome domain "lung function" (step 3). Alongside "lung function", the COMET category "respiratory, thoracic and mediastinal outcomes" contains additional outcome domains, such as, for instance, "acute exacerbations" or "cough". Appendix 4 contains additional examples.

This step-wise approach allowed us to assess the frequency and consistency of reporting, which we did at the level of outcome domains.

Step 4: Further following the COMET recommendations [17], we performed an additional content analysis of self-reported questionnaires that were completed by patients and that were used in the included studies to identify possible patient-reported outcome domains. We assessed questionnaires at the subdomain/subscale level. If at least one of the included articles mentioned subdomains/subscales of questionnaires in their results, we assessed the corresponding questionnaire in further detail. More specifically, we retrieved the questionnaires from the literature and extracted the measured concepts. Next, the same research steps were taken as mentioned above to classify and categorise the concepts into outcome domains. Similar or unique concepts were not counted separately. This analysis was done by four researchers, including three psychologists.

Results

Our search yielded 14 138 records. After removing duplicates, we assessed 7556 records, of which 5385 were excluded after the first screening phase. A total of 2125 full-text articles were screened, resulting in 428 eligible papers (figure 2).

Study characteristics

The characteristics of included papers are presented in table 1. Of the 428 included papers, a quantitative, qualitative and mixed-methods design was used in 406 (94.9%), 19 (4.4%) and three (0.7%) papers, respectively. From the 406 quantitative papers, 255 (63%) were retrospective cohort studies. The 428 included studies were conducted in 41 countries, of which 31 were done in more than one country. Studies were mainly conducted in Japan (24.3%), the USA (17.3%) and Italy (10.3%). Of all included PPF phenotypes, IPF was the most targeted disease (n=374) in the studies. The most common population among PPF was fibrotic HP (n=34), followed by fibrotic CTD-related ILD (n=27) and idiopathic fibrotic NSIP (n=27). Four studies did not specify which type of PPF was present in their sample. Involvement of patients or their advocates in setting up the studies, such as determining the study design and selecting the outcomes to be measured, was reported in only 3% of the included papers.

Extracted outcomes and domains

We extracted a total of 1685 outcomes, of which 1340 outcomes (79.5%) came from quantitative sources and 345 (20.5%) from qualitative sources. The inductive analysis of this long list of outcomes that were extracted verbatim from the eligible papers resulted in 83 outcome domains. The analysis of questionnaires identified one additional domain, resulting in a total of 84 outcome domains, as shown in figure 3, covering 20 COMET categories. In appendix 4, we provide an example of the COMET categories "respiratory, thoracic and mediastinal outcomes" and "emotional wellbeing" linked to the outcome domains and examples of outcomes as extracted from the papers. In the following sections, we detail the outcome domains based on quantitative and qualitative sources and questionnaire analysis.

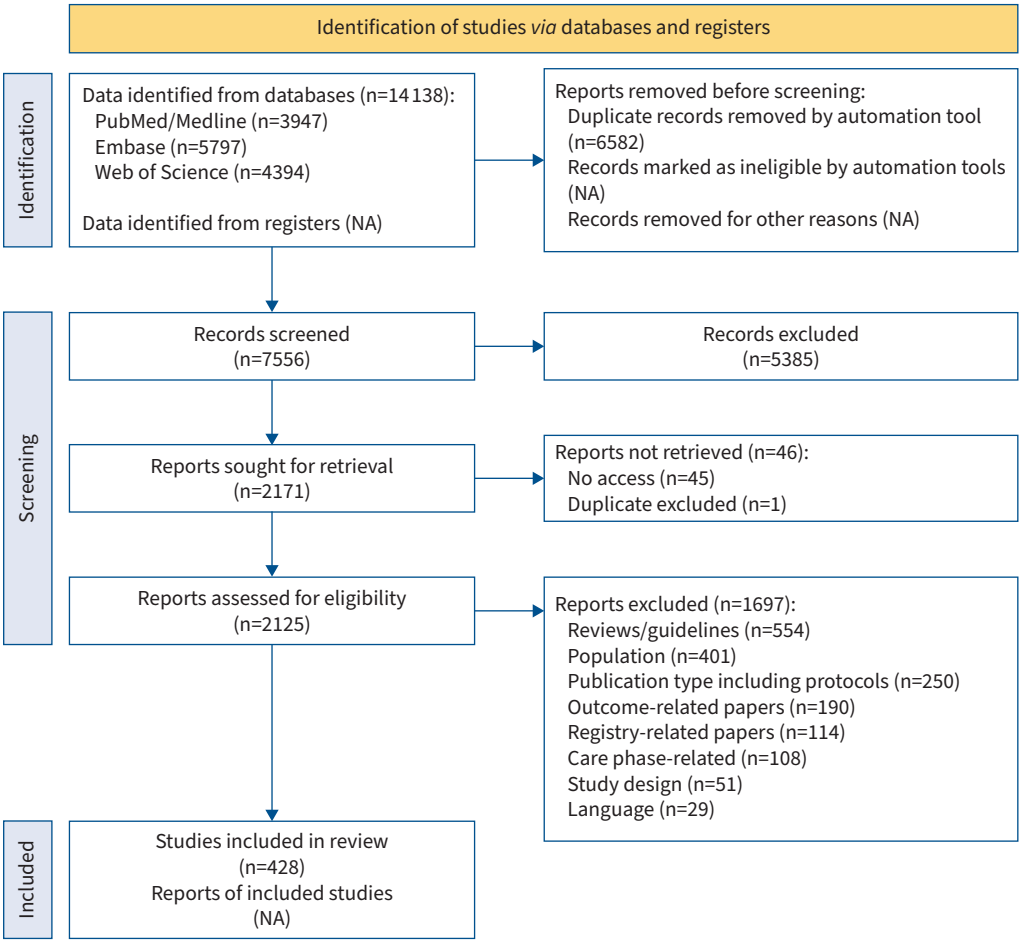

FIGURE 2 Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 flow diagram [43].

Outcomes, categories and domains from the quantitative source

Of the 1340 outcomes extracted from a quantitative source, most were classified in the COMET categories "respiratory-related outcomes" (n=372, 28%), "mortality/survival" (n=292, 22%) and "general outcomes" (n=226, 17%). When grouping the 1340 outcomes, we identified 64 outcome domains. Most of the outcomes referred to the outcome domains "all-cause survival" (n=237), "lung function" (n=164), "exercise capacity" (n=99), "side-effects/complications" (n=93) and "health-related quality of life (HRQoL)" (n=85). A comprehensive overview can be found in appendix 5.

Outcomes, categories and domains from the qualitative source

The 345 outcomes that were extracted from the qualitative sources were mostly classified in the COMET categories "emotional functioning" (n=134, 39%), "physical functioning" (n=49, 14%) and "respiratory-related outcomes" (n=44, 13%). Our analysis of qualitative outcomes yielded 51 outcome domains. The most frequently represented domains included "capability to do activities you enjoy" (n=31), "anxiety, worry and fear" (n=26), "dealing with disease progression" (n=25), "coping with the disease" (n=24) and "being knowledgeable about the disease and treatment" (n=24). Appendix 5 contains a detailed overview.

Concepts and domains from the questionnaire analysis

Among the 1340 quantitative outcomes, 261 outcomes (19%) were assessed using self-report questionnaires. These assessments were reported across 90 studies. More specifically, we assessed 49 questionnaires in detail and extracted a total of 122 concepts of patient health. These concepts referred the most to the following outcome domains: "capability to do activities you enjoy" (n=17), "health-related quality of life" (n=17), "fatigue" (n=9), "psychological wellbeing" (n=7) and "level of physical activity" (n=6). The questionnaire analyses yielded the additional concept "level of energy", which was not covered

TABLE 1 Characteristics of the included studies (n=428)

Characteristics of the included studies	
Design	
Quantitative design	n=406 (94.9%)
Nonexperimental	n=382
Cohort	n=336
Prospective cohort	n=82
Retrospective cohort	n=255
Case–control study	n=8
Cross-sectional study	n=36
Experimental	n=24
Randomised controlled trial	n=23
Quasi-experimental design	n=1
Qualitative design	n=19 (4.4%)
Mixed-methods design	n=3 (0.7%)
Countries	
Studies targeting a single country	n=397 (92.8%)
Studies targeting multiple countries	n=31 (7.2%)
Top 5 countries with the most publications:	
Japan	n=104 (24.3%)
USA	n=74 (17.3%)
Italy	n=44 (10.3%)
UK	n=39 (9.1%)
Korea	n=25 (5.8%)
Target population in studies	
IPF	n=375
PPF[#]	n=145
Fibrotic HP	n=34
Fibrotic CTD-related ILD	n=27
Idiopathic F-NSIP	n=27
Fibrotic sarcoidosis	n=14
PPFE	n=10
Fibrotic exposure-related ILD	n=9
Fibrosing organising pneumonia	n=2
Unclassifiable fibrotic ILD	n=20
Other (*e.g.*, familial pulmonary fibrosis)	n=2
Fibrotic ILD (not further specified)	n=4
Patient involvement in studies	
No	n=416 (97%)
Yes	n=12 (3%)

[#]: Grouping among progressive pulmonary fibrosis (PPF) cases was carried out according to Raghu *et al.* [2]. When a paper targeted multiple populations, each was taken into consideration separately. CTD: connective tissue disease; F-NSIP: fibrotic nonspecific interstitial pneumonia; HP: hypersensitivity pneumonitis; ILD: interstitial lung disease; IPF: idiopathic pulmonary fibrosis; PPFE: pleuroparenchymal fibroelastosis.

by the outcome domains previously identified in the quantitative or qualitative data sources and was hence added as an additional outcome domain (see appendix 6).

Differences between data sources

The Venn diagram in appendix 7 provides an overview of the source of the outcome domains. Overall, most of the outcomes (n=929, 69.3%) from the quantitative source were classified within the COMET core areas “physiological/clinical” and “death”, while most of the qualitative outcomes (n=260, 75.4%) referred to the COMET core area “life impact”. When looking at differences in the outcome domains between the quantitative and qualitative sources, we noticed that 35% (n=29) of the 83 outcome domains were reported in both sources, 40% (n=33) were mentioned in the quantitative papers only, while 25% (n=21) were only reported in the qualitative sources. Of these 21 domains from the qualitative literature, 11 were associated with the COMET category “emotional functioning”. Examples of domains only reported in qualitative sources are loss of independence, sexual intimacy, impact on relationship roles, loneliness, burden of side-effects and feelings of guilt. However, when taking into consideration the additional analysis of the questionnaires’ subdomains, seven domains were already covered, *i.e.*, loss of independence, sexual

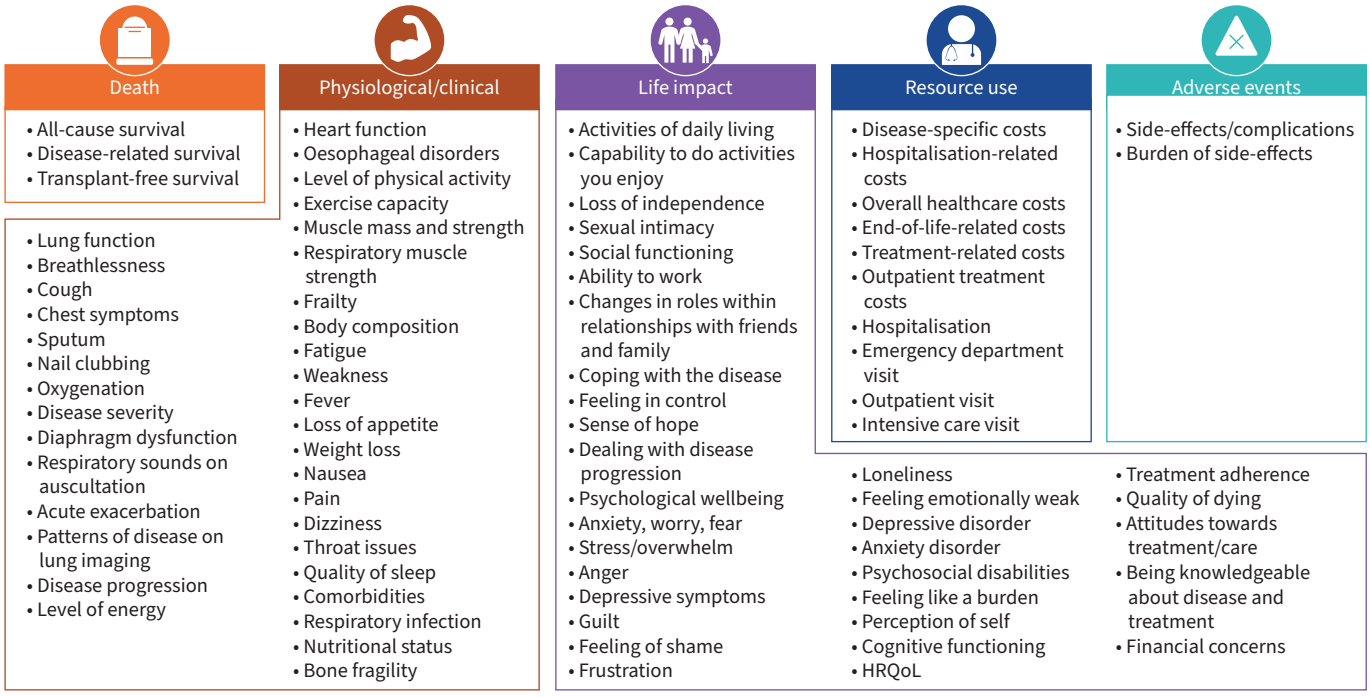

FIGURE 3 List of identified outcome domains, classified by COMET Core Areas. HRQoL: health-related quality of life.

intimacy, impact on relationships roles, feeling in control, dealing with disease progression, psychosocial disabilities and financial concerns. This means that 14 domains from the qualitative sources were not covered by other data sources (either quantitative or questionnaires), such as sense of hope, burden of side-effects, throat issues, feelings of shame, loneliness and weight loss.

Discussion

There is an increasing need for value-based healthcare as a driver for quality of care, which is also relevant for care practices for patients with IPF or other forms of PPF [31]. A key pillar of value-based healthcare is the assessment of outcomes that are relevant for patients to guide the transformation of healthcare practices [16]. This scoping review provides an extensive list of 84 outcome domains that are assessed in clinical research. Hence, this list can be considered a comprehensive basis to develop a COS containing a minimum set of outcomes that patients, their caregivers and healthcare professionals deem the most relevant to be used in the clinical care for patients with IPF or PPF.

The majority of included articles had a quantitative design (94.9%). Aligned with our expectations based on prior research, physiological and clinical outcomes were most commonly addressed. In fact, most of the outcomes were classified under the domains “all-cause mortality”, “lung function” and “exercise capacity”. The focus on physiologically and clinically relevant domains was also reflected in the COS developed by Saketkoo *et al*. [20]. This COS, designed in the context of a randomised controlled trial for patients with IPF or CTD-ILD included dyspnoea, lung imaging, lung physiology, survival, medications and HRQoL following a Delphi process [20]. While the importance of those physiologically and clinically related domains is out of question and these domains are also the most frequently used in clinical trials or guidelines, one may question, however, whether they are also the most important for patients and for challenging routine care practices. A multidisciplinary ILD committee has defined person-centred outcomes as a “collection of reliable and valid end-points that represent what matters most to individual patients in their day-to-day lives; these outcomes may represent how patients feel, or function, or how they view their QoL” [32]. Yet, “end-point” is a term usually used in research to measure an intervention’s effectiveness. In routine clinical care, however, the focus should be on the impact on patients [33]. This change in perspective is crucial to consider when developing a COS for clinical practice instead of trials. Indeed, careful consideration and selection of domains are important to not overlook what patients deem most important as there may be a gap between conventional metrics or end-points and those health outcomes that truly matter to patients [33]. Nonetheless, the abovementioned framework of person-centred outcome domains is an important step to support the shift to what matters to patients in research. The

following person-centred outcome domains were suggested to be considered in ILD research: HRQoL, symptoms, psychological and emotional wellbeing, functional status, oxygen needs, hospitalisations, survival, and acquisition of knowledge [32]. Our data covered the proposed domains, except for oxygen needs and acquisition of knowledge, as these domains were considered processes of care. Processes and structures of care are important in quality improvement initiatives, but within value-based healthcare, they are considered intermediate components rather than core outcomes [34]. Indeed, it is postulated that internal processes and structures of healthcare systems should not be the focus of COS. Nevertheless, they could be measured in parallel. Furthermore, the framework developed by Aronson *et al.* [32] is useful in guiding research, yet our aim was to obtain an extensive list of domains to be considered for a COS in routine care. Hence, our methodological approach and results differ from the framework, as we aimed to obtain a broader range of health aspects from multiple sources.

Hence, to capture potential patient-relevant domains, we also included qualitative papers as the resulting outcomes and outcome domains might reveal additional layers of experiencing and managing the disease [17, 35]. Our search was extensive, but surprisingly, only 4.4% (n=19) of the included articles had a qualitative design. Nonetheless, this resulted in 21 additional domains identified, mainly within the COMET category "emotional functioning". Although validated questionnaires or survey items can capture additional facets, as was also noted in our data, it remains crucial to continue elevating the patient's voice through qualitative methods as we still identified 14 domains not being covered by other data sources and to ensure that both data and stakeholder perspectives match. As an example, the related domains "coping with the disease", "dealing with disease progression", "sense of hope" and "feeling in control" were only addressed twice (0.2%) in the quantitative sources, but were reported in 17% (n=57) of the outcomes in qualitative sources. So, although coping is often brought up by patients, it remains unclear how this aspect is measured and addressed in routine care and research. This supports the importance of including qualitative data to inform the development of a COS for IPF/PPF routine care.

In addition to qualitative data, patient-reported outcomes from questionnaires are another crucial source for COSs to ensure patient-centredness as they capture important patient' views [36]. For the development of a COS, the COMET handbook supports the assessment of self-report questionnaires at a more granular level to extract potentially additional outcome domains [17, 37]. Despite the COMET recommendation, that patient-reported outcome measures should be appraised also at item-level, we deemed this not feasible for our review. Overall, we captured only one additional domain based on our subdomain analysis, which was "level of energy". During discussions with the patient partners within our consortium, it became clear that this concept differs from other concepts identified through other sources, such as, for instance, fatigue. Moreover, HRQoL was, not surprisingly, the most commonly measured concept in research papers. However, HRQoL is broadly recognised as an umbrella term for patient wellbeing. Prior research emphasising the patient perspective advocated to precisely define HRQoL components when determining a COS [38]. Hence, insights on individual HRQoL components are crucial, in order to be able to improve patients' wellbeing effectively.

Priorities between researchers, healthcare professionals and patients might differ when selecting clinical outcomes and outcomes of wellbeing. Therefore, patient involvement is another crucial component in research and COS development to truly align patients' needs with the research subjects and to increase the value of research [39–41]. Patient involvement is defined as "research being carried out with or by members of the public rather than to, about or for them" and refers to approaches such as collaboration, consultation and patient-led research [40]. From all included papers, only 12 (3%) mentioned involving patients in the research process. Although patient involvement is increasingly being considered, it was not clear whether study authors had involved patients in selecting the outcomes to be investigated. Hence, one may wonder whether the outcomes being addressed are truly reflect to the patients' needs. This issue aligns with the research presented by Saketkoo *et al.* [38], who showed that patients with IPF and CTD-related ILDs deemed outcomes important (cough, for instance) that were not withheld in a Delphi consensus exercise including healthcare professionals only. Of course, involving patients in each study may not be feasible. Nevertheless, when aiming towards patient-centeredness in research and clinical care, the involvement of patients in the development of a COS is essential.

Methodological considerations

This scoping review was deliberately broad to obtain a wide perspective on outcome domains to be considered for a COS to be used in the clinical care provided to patients with IPF/PPF. The most important strength of the review is the highly multidisciplinary collaboration between researchers, clinicians and patient representatives. Also, we used a prevailing and comprehensive systematic methodology to conduct

our scoping review, which was further supported by the COMET guideline and taxonomy. Some considerations, however, are worth noting.

There is no clear guideline as to how to identify outcome domains from outcomes and multiple classifications exist, such as the COMET taxonomy, which we used [30]. We noticed that the COMET domains were too broad to categorise the outcomes we extracted. Hence, we followed a consensus-based approach using qualitative methodology to create meaningful outcome domains within each COMET category. This iterative process was executed by researchers with multiple professional backgrounds, while involving patient representatives to capture their perspectives. However, given that there is no taxonomy available for domains on a more detailed level, this approach might have introduced bias. We also made some slight adaptations on how to use the COMET taxonomy. More specifically, for adverse events or side-effects, it is recommended to classify specific adverse events within the COMET taxonomy with an additional level referring to the adverse events category. However, we decided not to classify individual adverse events or side-effects, but to keep them in the overall adverse event category due to feasibility reasons. We applied the same principle to comorbidities. Also, we encountered challenges in making clear distinctions between outcomes and processes of care. As a result, few outcomes were classified in the COMET categories "delivery of care" and "need for further intervention". Since the COMET taxonomy is mainly used in clinical trial settings, these adaptions needed to be made in order to find a balance between the COMET classification requirements and our project's aim and methodology.

Furthermore, our list is now based on outcome domains from the literature. Although we have included qualitative research to capture patient experience, this list warrants further discussion with stakeholders to assess whether all domains are relevant or whether we have missed domains that might be relevant for clinical care.

Moreover, at this stage, we did not count the individual outcomes reported in articles as the purpose of the present paper was to provide an overview of outcome domains. For example, one of our domains is disease progression, a broad domain that may be defined differently by researchers or guidelines. Therefore, we also captured the specific definition of disease progression. Moreover, we identified 12 different instruments to assess HRQoL and five to measure depression. Overall, this diversity of measurement instruments may pose a challenge for extrapolation and benchmarking of results for interventions in clinical care and research, which has already been investigated for clinical trials [37]. This assessment of outcome reporting heterogeneity is an important starting point for further research, that we will undertake in later stages of our COS development when aiming to determine the most appropriate measures to capture the core outcomes [42].

Regarding our eligibility criteria, we excluded clinical drug trials and registry-related papers as these are part of a different subanalysis. We also excluded clinical drug trials in this analysis as it is not clear whether the context of clinical trials also applies to clinical care and whether changes are required in the content of the COS. Indeed, clinical trials focus mainly on end-points for a particular intervention, whereas in clinical care health outcomes are addressed across the entire cycle of care. This introduces an important reflection regarding the definition of outcomes, as the term is often used interchangeably with end-points or even measures [33]. We also excluded biomarkers as these are also considered intermediate health indicators. Moreover, we excluded systematic reviews, including reviews summarising symptoms, patient-centred outcomes or supportive needs, as these already may include author bias.

Lastly, most of the included papers targeted the IPF population, which is not surprising, given that the PPF classification is relatively new and that IPF is the most studied fibrosing ILD so far [1]. However, patients with progressive fibrosis have similar needs and therefore, when developing a COS for this group of patients, their input will be crucial, as previously published literature might have investigated mixed populations without focusing on the common needs of patients with IPF or PPF.

Conclusion

In conclusion, we identified 84 outcome domains addressed in clinically related research on IPF and/or PPF that could be included in a COS for routine care. Ultimately, focusing on patient-relevant outcomes is crucial to evaluate healthcare effectiveness from the patients' perspective and thus drive changes in quality of care [34]. This requires a change in mindset. Therefore, having a list of domains that is more comprehensive than those used in trials or conventional research is an important starting point, as some domains receive less attention in research or guidelines but may be relevant to consider in routine care, such as cognitive functioning, coping or other life impact-related domains. This emphasises the importance of including qualitative research, patient-reported outcomes and patient involvement in developing a list of

domains. However, there is still the need to investigate which domains are considered most relevant for patients to minimally assess in routine care throughout the care cycle. This scoping review is a first step in our COCOS-IPF (Co-designing a Core Outcome Set for and with patients with IPF) project, which aims to develop a COS for use in routine care of patients with IPF and PPF. In a next step, we will prioritise the list with domains using a consensus process.

Points for clinical practice

- The outcomes identified in this scoping review, spanning diverse domains, highlight the complexity of needs and experiences of patients with IPF/PPF.
- Future research can build on the results of this scoping review to develop, test and implement a COS to improve IPF/PPF clinical care and to better understand and incorporate the needs of IPF/PPF patients.

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