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Scout – sarcoidosis outcomes taskforce. A systematic review of outcomes to inform the development of a core outcome set for pulmonary sarcoidosis

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Abstract. Background: Clinical trials evaluating different management strategies for pulmonary sarcoidosis may measure different outcomes. This heterogeneity in outcomes can lead to waste in research due to the inability to compare and combine data. Core outcome sets (COS) have the potential to address this issue and here we describe a systematic review of outcomes as the first step in the development of a COS for pulmonary sarcoidosis research. **Methods:** A search of clinical trial registries for phase II, III and IV trials of pulmonary sarcoidosis was undertaken along with a rapid review of the patient perspective literature. Each study was screened for eligibility and outcomes extracted verbatim from the registry entry or publication then reviewed, grouped and categorised using the COMET taxonomy. **Results**: 36 trial registry entries and 6 studies on patients' perspective of pulmonary sarcoidosis were included reporting 56 and 82 unique outcomes respectively across 23 domains. The most frequently reported outcome domain was "respiratory, thoracic and mediastinal outcomes". However, the patients' perspective literature identified outcomes in the "personal circumstances" and "societal/carer burden" domains that were not reported in any of the included trial registrations. **Conclusions:** Using both clinical trial registry data and published literature on patients' perspective has allowed rapid review of outcomes measured and reported in pulmonary sarcoidosis research. The use of multiple sources has led to the development of a comprehensive list of outcomes that represents the first step in the development of a COS for use in future pulmonary sarcoidosis research.

Key words: Pulmonary sarcoidosis, Systematic review, Core outcome set, Outcomes

Background

Sarcoidosis is a systemic granulomatous disease of unknown etiology. Sarcoidosis can affect any organ but most commonly affects the lungs with lung involvement observed in more than 90% of sarcoidosis patients (1, 2). Pulmonary sarcoidosis may cause

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significant pulmonary symptoms, pulmonary dysfunction, and life-threatening complications such as pulmonary hypertension and end-stage pulmonary disease. The management of pulmonary sarcoidosis is aimed at preventing/controlling organ damage, relieving symptoms, and improving the patient's quality of life.

Clinical trials evaluating the effectiveness of different management strategies often measure different outcomes. This heterogeneity not only has an impact on the ability to compare and combine data but may also mean that outcomes considered to be the most meaningful to patients, health professionals and researchers are not measured and reported. Core outcome sets, defined as "the minimum (set of outcomes) that should be measured and reported in all clinical trials of a specific condition" (3), have the potential to address outcome heterogeneity and subsequently research waste.

Some work towards harmonisation of outcomes, in pulmonary sarcoidosis research, has already been undertaken but not without limitations. Kampstra *et al* (4) have reported a COS for pulmonary sarcoidosis. However, the decision to include outcomes was made by an expert panel of health professionals with no direct input from patients. Baughman *et al* (5) have also reported a set of outcomes and whilst this study included patients their input was limited to ranking seven outcomes that had been previously agreed by health professionals.

The Sarcoidosis Core Outcomes Taskforce (SCOUT) study will build on this previous work and develop a core outcome set (COS) for pulmonary sarcoidosis that includes input from clinicians, patients and researchers in the field, as a minimum, in line with the COS-STAD recommendations (6). This systematic review represents the first stage of COS development. It aims to identify all outcomes reported in registered clinical trials for pulmonary sarcoidosis and in literature exploring the experiences of patients who have pulmonary sarcoidosis.

Methods

Information sources

Outcomes were identified from two sources: registered clinical trials and published literature of patient experience. Separate searches were undertaken for each source and the methods for each are described below. We did not perform an assessment of study quality for either sources as the purpose of this review was to summarise outcomes reported only.

Registered clinical trials

Search strategy

On the 26th March 2019 three trial registries, the ClinicalTrials.gov database (7), ISRCTN registry and the International Clinical Trials Registry Platform (ICTRP), were searched to identify phase II, III and IV trials of pulmonary sarcoidosis (Table 1).

Eligibility Criteria

Registry entries of randomised phase II, III and IV trials of therapeutic interventions for patients with pulmonary sarcoidosis were included.

Trials were excluded if they met any of the following criteria: phase I trials, trials of treatments for other sarcoidosis types, trials for the treatment of pulmonary hypertension, trials focusing on the diagnosis and not treatment of pulmonary sarcoidosis, publications in any language other than English.

Data extraction – registered clinical trials

Data on study characteristics including the year of registration, geographical region of work, planned sample size, duration or follow up and trial phase was extracted by one reviewer (NLH).

Data on outcomes listed in the trial registration entry was extracted verbatim by two reviewers (NLH and SLG) from the specific outcome fields and from the study information free text. The reviewers extracted outcomes from ten randomly selected studies in duplicate. The outcomes were reviewed for consistency and then the remaining studies were split 50:50 between reviewers. Where composite outcomes were used, all component outcomes were included. Where an outcome was reported in terms of the measurement instrument used, for example a particular questionnaire, the instrument was reviewed, and outcomes extracted from the instrument domains. Each outcome was entered in a separate row of an excel spreadsheet.

Patient experience – narrative synthesis

Search strategy

Rapid review methodology (8, 9) was used to search the MEDLINE database on the 19th November 2019 with no restrictions on date. The search terms, described in Table 1, comprise empirically tested qualitative methodological filters designed to identify qualitative research from the MEDLINE electronic database with the best balance of sensitivity and specificity (10).

Eligibility

Studies reporting findings of the views and experiences of people with pulmonary sarcoidosis, on their condition and treatment were eligible for inclusion. Studies that involved participants with sarcoidosis affecting other organs, in addition to the lungs, were included.

Data Extraction – narrative synthesis

Data on study characteristics, including the year of publication, geographical region of work, methods used and participants, were extracted by one reviewer (NLH).

We took a deductive approach to identifying outcomes in the text, identifying text excerpts that could be interpreted as relevant to pulmonary sarcoidosis outcomes. For example, we included reports about how patients felt or functioned in relation to their pulmonary sarcoidosis. Outcomes were extracted verbatim from all text, in the results and discussion sections, which included participants' quotations about their views or experiences and from authors' commentary. Surveys of participant experience were also included, and outcomes extracted from the survey content. Each outcome was entered in a separate row of an excel spreadsheet.

Outcomes were extracted in duplicate by two reviewers (NLH and SLG).

Assessment of Eligibility

Two authors (NLH and SLG) reviewed 50% of studies (identified from both search strategies) in duplicate with regular batch checks for consistency and to discuss any studies where there was disagreement, the remaining 50% of studies were then reviewed independently (NLH 25%, SLG 25%). Where either reviewer was uncertain about inclusion of a study this was discussed by both reviewers. No study required third reviewer arbitration.

Outcome Classification

Outcomes were categorised, by NLH and SLG, according to the COMET taxonomy of core domains (11). This taxonomy comprises 38 domains under five areas (mortality, physiological/clinical, life impact, resource use and adverse events). Classification of outcomes under the domains, and the grouping of outcomes was checked by a sarcoidosis specialist (DAC).

Table 1. Search Strategy

ClinicalTrials.gov, ISRCTN and ICTRP search strategy	
Condition:	Sarcoidosis
Study type:	Interventional: Clinical Trial
Study phase:	Phase II, III and IV
Recruitment stage:	Recruiting/Completed; Not yet recruiting; Unknown
MEDLINE search strategy	
Multi-Field Search	
	sarcoidosis.ab
AND	patient*.ab
AND	((interview: OR experience:).mp OR qualitative.tw.)
AND	(symptom OR treatment OR living with).ab

Results

Search results and study characteristics

The search of trial registries returned 129 entries that were screened for eligibility, of which 36 were included. The MEDLINE search of the patients' perspectives literature returned 238 articles of which 6 were included. The flow diagram of included trials is shown in Figure 1. (A full list of included studies is available in supplementary file 1, this was reviewed by an expert steering committee to confirm that no key trials were missing. See Appendix).

After the MEDLINE search of patient perspective literature had been completed we identified an article by Van Helmondt *et al* that specifically

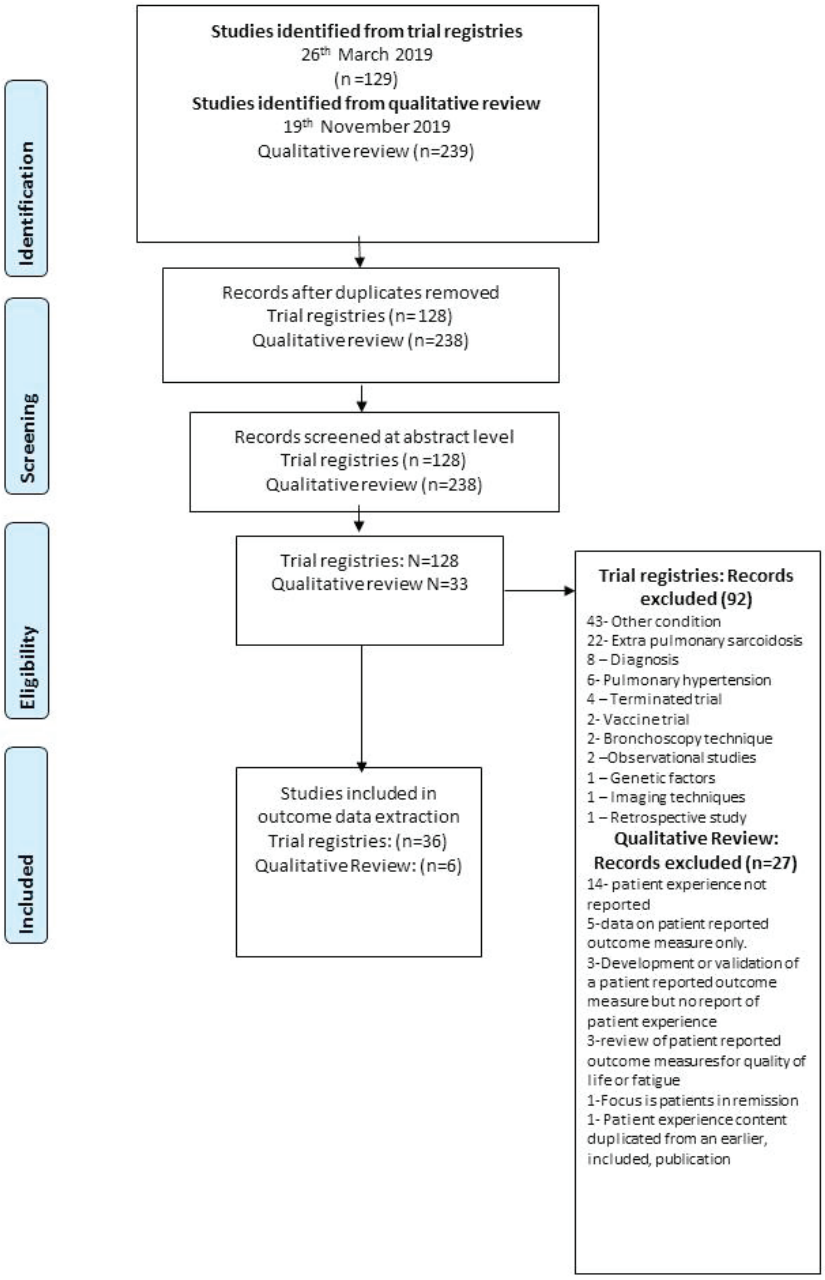

Figure 1. PRISMA flow diagram

explored published literature about patient perspectives of sarcoidosis (12). We repeated the search strategy of Van Helmondt *et al* in PubMed with no restrictions on date, no additional eligible studies were identified.

The characteristics of included trial registrations and patient perspective studies are shown in Table 2 and Table 3.

Table 2. Description of included trial registrations

Year of registration	**N (%)**
1999-2005	4 (11)
2006	4 (11)
2007	2 (5)
2008	3 (8)
2009	3 (8)
2010	2 (5)
2011	1 (3)
2012	1 (3)
2013	3 (8)
2014	4 (11)
2015	1 (3)
2016	2 (5)
2017	3 (8)
2018	3 (8)
2019	1 (3)
Phase	
I and II	3 (8)
II	14 (38)
II and III	4 (11)
III and IV	5 (14)
IV	11 (30)
Planned enrolment (median and range)	36 (10-180)
Region of work[a]	
Asia	2 (5)
Europe	11 (30)
North America	26 (70)
South America	0 (0)
Africa	0 (0)
Central America	0 (0)
Australasia	1 (3)
Duration of follow up in weeks (median and range)	26 (4-260)[b]

[a]Number exceeds total as a number of studies were conducted across multiple geographical areas.
[b.] One study did not report the duration of follow up

Outcomes reported in trial registry entries

A total of 364 individual outcomes, representing 56 unique outcomes, were extracted from trial registry entries with a median of 7 outcomes per trial (range 1-27). Each outcome was reviewed and categorised using the COMET taxonomy (Table 4).

No single outcome was measured and reported in all of the included studies. The majority of studies (89%) included one or more outcomes in the "Respiratory, thoracic and mediastinal outcomes" domain. Outcomes in this domain were measured by 33 studies, with a median of 4 "Respiratory, thoracic and mediastinal outcomes" per study (range 1-10). This domain included 146 individual outcomes and 10 unique outcomes including "pulmonary function" (33%), "disease activity and progression" (27%), "radiographic outcomes (9%) and "dyspnea-shortness of breath" (9%) (Table 5). The large number of individual outcomes compared to the unique outcomes reflects multiple methods of assessment for each of the overarching generic outcomes. For example, forced vital capacity, diffusing capacity of the lung for carbon monoxide, resting partial pressure of oxygen in the artery blood (PaO2) and spirometry were all included in the broader outcome of "pulmonary function".

The resource use outcome domains "economic outcomes" and "need for intervention" were reported only in clinical trial registry entries, albeit infrequently. No outcomes were reported in the "hospital" category which may reflect variability in the need for hospitalisation depending on the stage of disease.

Outcomes identified from patient perspective literature

The patient perspective literature included perspectives from 3169 patients and reported 179 individual outcomes (82 unique outcomes), with a median of 17 outcomes per study (range 10-97). A large number of outcomes (n=97 individual outcomes) were extracted from the work of Victorson *et al* who conducted two focus groups with patients (n=22) and undertook detailed coding of transcripts to develop a conceptual model of health-related quality of life. A summary of the included studies is provided in Table 3.

Patient perspective studies were more likely to include participants with experience of extra

Table 3. Summary of included patient experience studies

Study ID	Year of publication	Study Location	Participants	Data Collection Method	Number of outcomes identified
Swayze (18)	1991	USA	Not specified	Development of a self-help group – meeting to discuss topics that should be covered.	27
Patel *et al* (15)	2013	UK	23 (organ involvement: Lung n=22, skin=7 skin, eye n=7)	face-to-face semi-structured and cognitive interviews	14
Victorson *et al* (19)	2014	USA	22 (organ involvement: lung n=10, skin n=7 and eye n=5)	Focus Groups	97
Baughman *et al* (5)	2018	Online and available in multiple languages	1842 (692 Dutch, 528 German, 338 English, 148 Italian, 107 Spanish and 29 French).	Online survey	10
Moor *et al* (20)	2018	Netherlands	210 patients and 132 patient partners/carers	Interactive live survey	20
Voortman *et al* (21)	2019	Denmark Germany Netherlands	1072 (organ involvement: lung n=770)	Online survey	14

Table 4. Comparison of clinical trial registration outcomes and qualitative literature outcomes by domain.

Outcome Domain	Trial registry entries (n=38)		Qualitative studies (n=6)	
	Total number of unique outcomes within domain (number of verbatim outcomes)	Number of studies reporting one or more outcomes in the domain (%)	Total number of unique outcomes within domain (number of verbatim outcomes)	Number of studies reporting one or more outcomes in the domain (%)
1. Mortality/survival	1 (1)	1 (3)	1(1)	1 (17)
2. Blood and lymphatic system outcomes	1 (1)	1 (3	0 (0)	0 (0)
3. Cardiac outcomes	1 (2)*	2 (5)	1 (1)	1 (17)
4. Congenital, familial and genetic outcomes	0 (0)	0 (0)	0 (0)	0 (0)
5. Endocrine outcomes	0 (0)	0 (0)	0 (0)	0 (0)
6. Ear and labyrinth outcomes	0 (0)	0 (0)	0 (0)	0 (0)
7. Eye outcomes	1 (5)*	5 (14)	1 (17)*	5 (83)
8. Gastrointestinal outcomes	0 (0)	0 (0)	1 (5)	2 (33)
9. General outcomes	8 (37)	17 (46)	9 (23)	6 (100)
10. Hepatobiliary outcomes	0 (0)	0 (0)	0 (0)	0 (0)
11. Immune system outcomes	1 (14)	9 (24)	1 (1)	1 (17)
12. Infection and infestation outcomes	1 (2)	1 (3)	0 (0)	0 (0)
13. Injury and poisoning outcomes	0 (0)	0 (0)	0 (0)	0 (0)
14. Metabolism and nutrition outcomes	0 (0)	0 (0)	0 (0)	0 (0)
15. Musculoskeletal and connective tissue outcomes	0 (0)	0 (0)	6 (8)	2 (33)
16. Outcomes relating to neoplasms: benign, malignant and unspecified (including cysts and polyps)	0 (0)	0 (0)	0 (0)	0 (0)

Outcome Domain	Trial registry entries (n=38)		Qualitative studies (n=6)	
	Total number of unique outcomes within domain (number of verbatim outcomes)	Number of studies reporting one or more outcomes in the domain (%)	Total number of unique outcomes within domain (number of verbatim outcomes)	Number of studies reporting one or more outcomes in the domain (%)
17. Nervous system outcomes	1 (1)	1 (3)	2 (2)	2 (33)
18. Pregnancy, puerperium and perinatal outcomes	0 (0)	0 (0)	0 (0)	0 (0)
19. Renal and urinary outcomes	1 (1)	1 (3)	1 (1)	1 (17)
20. Reproductive system and breast outcomes	0 (0)	0 (0)	0 (0)	0 (0)
21. Psychiatric outcomes	3 (3)	2 (5)	3(7)	4 (67)
22. Respiratory, thoracic and mediastinal outcomes	10 (146)	33 (89)	12 (22)	6 (100)
23. Skin and subcutaneous tissue outcomes	1 (6)*	6 (16)	1 (18)*	4 (67)
24. Vascular outcomes	0 (0)	0 (0)	0 (0)	0 (0)
25. Physical functioning	5 (23)	13 (35)	8 (14)	4 (67)
26. Social functioning	1 (18)	12 (32)	3 (7)	4 (67)
27. Role functioning	5 (16)	7 (19)	7 (9)	3 (50)
28. Emotional functioning/wellbeing	3 (20)	15 (41)	12 (16)	6 (100)
29. Cognitive functioning	1 (2)	2 (5)	3 (4)	3 (50)
30. Global quality of life	2 (6)	5 (14)	1 (1)	1 (17)
31. Perceived health status	1 (12)	6 (16)	1 (1)	1 (17)
32. Delivery of care	5 (11)	9 (24)	2 (3)	2 (33)
33. Personal circumstances	0 (0)	0 (0)	4 (6)	4 (67)
34. Economic	1 (1)	1(3)	0 (0)	0 (0)
35. Hospital	0 (0)	0 (0)	0 (0)	0 (0)
36. Need for intervention	1 (1)	1 (3)	0 (0)	0 (0)
37. Societal/carer burden	0 (0)	0 (0)	1 (3)	2 (33)
38. Adverse events/effects	1 (35)**	19 (51)	1 (9)	5 (83)

*For the purpose of the Delphi survey outcomes considered to be extra-pulmonary organ involvement were grouped into one larger unique outcome "extra pulmonary organ involvement" rather than more granular outcomes within the domain.
** Some studies included treatment specific adverse events. However, for the purpose of the Delphi survey adverse events were grouped under a "side effects of treatment " outcome .

pulmonary organ involvement/ impairment. This is reflected in the range of outcomes included in the physiological/clinical core domain. In particular, gastrointestinal and musculoskeletal outcomes were only measured in patient perspective studies and the proportion of eye, nervous system, cardiac and skin and subcutaneous outcomes was higher when compared to the trial registry entries.

Two outcome domains in the life impact core domain, "societal/carer burden" and "personal circumstances", were only reported in qualitative studies. The societal/carer burden outcomes focused specifically on the impact on patients' partners whilst outcomes in the personal circumstances domain focused on the social support available to patients from family and friends and the impact of sarcoidosis on their relationships and personal finances.

All six of the included qualitative studies included outcomes in the "respiratory and thoracic outcomes", "general outcomes" and "emotional functioning" domains. However, compared to trial registry entries outcomes in the "respiratory and thoracic

Table 5. Respiratory, thoracic and mediastinal outcomes

Generic Outcome	Clinical trials.gov			Qualitative review	
	Number of studies reporting outcome (% of 33 studies)	Number of individual study outcomes grouped into generic outcome	Examples of study reported outcomes grouped into the generic outcome	Number of studies reporting outcome (% of 6 studies)	Text contributing to outcome grouping
Chest pain*	0 (0)	-	-	2 (33)	Chest pain
Chest tightness	0 (0)	-	-	1 (17)	" This included: **chest tightness, choking, congestion,** . . ."
Choking	0 (0)	-	-	1 (17)	
Congestion	0 (0)	-	-	1 (17)	
Cough	1 (3)	1	Cough	4 (67)	""It's mostly a dry cough, just a constant coughing.'"
Disease Activity/ progression	9 (27)	33	Clinical deterioration, Lupus Pernio Physician's Global Assessment, assessment of disease severity and activity, Pulmonary Sarcoidosis Flares, The Steroid Sparing Period, Time to Disease Progression, Symptoms, episodes of acute exacerbation, clinical worsening, stabilization, improvement or resolution of the disease, Observation group crossover to treatment group, Cumulative dose of prednisolone, Prednisolone dose between relapse and no relapse groups, Relapse or treatment failure, Sarcoidosis Treatment Score (STS) -prednisone dosage, serum angiotensin converting enzyme (ACE) concentration, Remission	1 (17)	stress/fear/anxiety (e.g., **fear of disease/ dying,** not being calm)
Dyspnea	3 (9)	16	activities that are caused or limited by breathlessness (St Georges Respiratory Questionnaire), Dyspnoea (ATS dyspnea scale), Dyspnea (Borg's CR10), everity of their shortness of breath before and after treatment, Improvement in dyspnea score	5 (88)	(). . . a range of health topics that included breathlessness, other respiratory symptoms. . . () "For patients, the most frequently coded statements were related to shortness of breath" "Difficulty breathing"
Functional Exercise capacity	7 (21)	14	Cardiopulmonary exercise testing (VO2max), 6-min walk distance (6MWD), Maximum incremental ventilatory performance test (MIVP)	2 (33)	exercise intolerance, reduced exercise capacity
Oxygenation	1 (3)	2	Blood gas analysis (AaDO2)	0 (0)	-

(Continued)

Generic Outcome	Clinical trials.gov			Qualitative review	
	Number of studies reporting outcome (% of 33 studies)	**Number of individual study outcomes grouped into generic outcome**	**Examples of study reported outcomes grouped into the generic outcome**	**Number of studies reporting outcome (% of 6 studies)**	**Text contributing to outcome grouping**
Pulmonary Function	11 (33)	45	Pulmonary function, Forced Vital Capacity, VO2 peak, endurance time at 75% of VO2 peak, Total Lung Capacity, Spirometry, pulmonary function studies, functional capacity, pulmonary status, lung function, Forced Expiratory Volume, Diffusion capacity of Lung for Carbon monoxide	1 (17)	blood tests/pulmonary function tests
Pulmonary inflammation	2 (6)	9	Exhaled nitric oxide and carbon monoxide, severity of lung inflammation, chest X ray, computed tomography, positron emission tomography (PET) scan, pulmonary tissue inflammation.	0 (0)	-
Pulmonary physiology	1 (3)	1	composite physiologic index	0 (0)	-
Radiographic outcomes	3 (9)	17	HRCT (Oberstein score), chest x-ray, chest imaging, computed tomography scan, radiographic parameters, radiographic success, overall response defined as combined clinical and radiographic parameters, FDG-PET outcomes	1 (17)	imaging
Respiratory symptoms	3 (9)	8	Respiratory symptoms (St Georges Respiratory Questionnaire)	1 (17)	(). . . a range of health topics that included breathlessness, other respiratory symptoms. . .()
Wheezing*	0 (0)	-	-	1 (17)	"This included: chest tightness, choking, congestion, cough, dyspnea, exercise intolerance, and **wheezing.**"

*wheezing and chest pain are included in the St Georges Respiratory questionnaire and are included in the "respiratory symptoms" generic outcome. They have been listed separately here as they were specifically mentioned in the included qualitative research where as trials reported "respiratory symptoms" as an outcome rather than the individual symptoms assessed by the PROM.

Table 6. Patient Reported Outcome Measures identified from clinical trial registry entries.

PROM	PRO concept based on Thunhold et al (13)	Number of clinical trial registry entries reporting the use of the PROM (%)	Taxonomy domains included in the PROM domains.												
			Physiological/clinical						Life impact						
			Eye outcomes	General Outcomes	Psychiatric Outcomes	Respiratory, thoracic and mediastinal outcomes	Physical Functioning	Skin and subcutaneous tissue outcomes	Social Functioning	Role functioning	Emotional functioning/ wellbeing	Cognitive Functioning	Perceived health status	Delivery of care	Personal Circumstances
EuroQoL - EQ5D	Health Status and quality of life	1 (3)		X	X		X								X
Fatigue Severity Scale	Fatigue	1 (3)		X			X		X	X	X				
FACIT-Fatigue Scale	Fatigue	1 (3)		X			X		X		X				
Fatigue Assessment Scale	Fatigue	1 (3)		X								X			
Modified MRC Dyspnea Scale	Dyspnea	1 (3)				X									
Borg's CR10	Dyspnea	2 (6)				X									
Leicester Cough Questionnaire	Health Status and quality of life	2 (6)					X		X		X				
Sarcoidosis Health Questionnaire	Health Status and quality of life	4 (11)					X				X				
Kings sarcoidosis questionnaire	Health Status and quality of life	5 (14)	X	X		X		X						X	
SF36	Health Status and quality of life	6 (17)		X			X		X	X	X		X		
Saint Georges Respiratory Questionnaire	Health Status and quality of life	8 (22)				X			X		X				

domain" were more frequently related to symptoms "dyspnea – shortness of breath" (83% of studies), "cough" (83%) and less frequently to "pulmonary function" (17%) (Table 5). In the "general outcomes" domain "fatigue" was the most frequently reported outcome (30% of outcomes) and was assessed in five of the six included studies. In the clinical trial registrations, 90% of outcomes in the "emotional functioning" domain were reported as "emotional wellbeing"; in contrast, patient perspective studies were more specific in the outcomes reported within this core domain for example, "fear of disease progression", " mood" and "embarrassment".

Patient perspective studies were also more likely to assess outcomes in the "life impact" core domain with the exception of "global quality of life" and "perceived health status". The frequency of outcomes in these two domains may be a result of more granular outcomes being reported that contribute to these broader states for example "fatigue".

Use of Patient Reported Outcome Measures

Eleven patient reported outcome measures (PROMs) were identified from the registered studies in clinicaltrials.gov. The domains assessed in each PROM were extracted and included in Table 4 for each trial reporting the use of the PROM. A summary of the frequency of PROM use and the domains assessed is provided in Table 6.

Thunhold et al have reviewed PROMs used in pulmonary sarcoidosis research and from 124 studies identified 66 different PROMs (13) with "health status and quality of life" the most frequently assessed patient reported outcome concept. In the present study "health status and quality of life" was also the most frequently reported concept, assessed in 26 (70%) trial registry entries using six different PROMs (Table 6).

Discussion

This review highlights the heterogeneity in outcomes measured and reported in pulmonary sarcoidosis research. It represents the first step in the development of a core outcome set and has identified outcomes from two key sources, registered clinical trials and studies that have explored patients' perspectives.

Using clinical trials alone has the potential to overlook outcomes relevant to patients (14). However, methods to include the patient perspective such as patient interviews and focus groups can be resource intensive. The rapid qualitative review approach (9), utilised in the present study, has incorporated evidence from a large number of patients into the early stages of COS development and has identified outcomes that would have been overlooked in a review of clinical trial registrations alone. The patient perspective, and diversity of included patients, has also contributed to understanding of outcomes relating to extra-pulmonary organ involvement and provided further detail on outcomes such as emotional wellbeing.

Reviewing available literature on the patient experience also has the potential to include the patient perspective from a wide geographical range including low and middle income countries. In the case of pulmonary sarcoidosis there were a small number of studies that sought the patient perspective (n=6) and the geographical representation of patients was limited to the USA and Europe.

The large overlap between outcomes reported in registered trials and in the patients' perspectives literature may in part be due to the use of PROMS by 50% of the included trials. Indeed data was included from a study by Patel *et al* that reported qualitative data from the first stages of the development of the Kings Sarcoidosis Health Questionnaire (15). In the present study eleven PROMs were reported by included trials representing a small proportion of that been used in published sarcoidosis research (13). This may in part be due to included observational studies that, depending on year of publication, may not have been included in a trial registry. Heterogeneity not only in the choice of outcomes but also in the method and quality of outcome assessment poses challenges for evidence synthesis and "how" to measure will be important to address in the next steps following consensus on what outcomes are the most important to measure(16, 17).

Previously developed core outcome sets for pulmonary sarcoidosis have involved clinical stakeholders only. Kampstra *et al* report a seven outcomes that include: mortality; pulmonary function; soluble interleukin-2receptor (sIL-2R) change as an activity biomarker; weight gain; quality of life/physical functioning; osteoporosis; and clinical outcome status(4). In the present study outcomes relating to side effects of treatment (osteoporosis and body weight), mortality, and disease progression (clinical outcome status) were reported by both clinical trials and patient perspective studies. However, from the perspective of patients, other respiratory outcomes such as "dyspnea" and "cough" were reported more frequently than "pulmonary function". Kampstra *et al* recommend measuring "quality of life and physical functioning" outcome domains using the Kings Sarcoidosis Questionnaire and Fatigue Assessment Scale respectively, however, these may not fully capture outcomes important to patients such as personal circumstances, social functioning and emotional functioning domains that impact on overall quality of life.

Conclusion

The present study has identified outcomes reported in registered clinical trials for pulmonary

sarcoidosis and in literature exploring the experiences of patients who have pulmonary sarcoidosis. Trials frequently measured outcomes in the "Respiratory, thoracic and mediastinal outcomes" domain and this was echoed in the patient experiences. However, no one outcome or outcome domain was measured in all clinical trials. This heterogeneity in the outcomes measured and reported in clinical trials for pulmonary sarcoidosis impacts on the ability to compare and combine evidence. Systematically reviewing both clinical trial registrations and patient perspective literature is an efficient way to generate a comprehensive list of outcomes as the first step in the development of a core outcome set for pulmonary sarcoidosis that will seek consensus from patients and health professionals , researchers in the field and industry representatives.

Abbreviations: COMET – Core Outcome Measures in Effectiveness Trials; COS - Core Outcome Set; PROM – Patient Reported Outcome Measure

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: NLH, SLG, PRW, RPB, MAJ, NAK, DEV, JCG, DAC have no competing interests. ESB is an employee of Janssen Research and Development, LLC, who has sponsored research studies in Sarcoidosis. EJS is an employee of Insmed Incorporated. MW employee of Janssen Research & Development. HJ is a sarcoidosis patient. TA-H, HN and NS were employed by the funder (The Foundation for Sarcoidosis Research) during the research.

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Authors' contributions: NLH: Conceived and designed the analysis. Performed the search, extracted and categorised outcomes. Drafted the manuscript. SLG: Conceived and designed the analysis. Performed the search, extracted and categorised outcomes. Reviewed and approved the manuscript. PRW: Conceived and designed the analysis. Supervised the project. Reviewed and approved the manuscript. DAC: Contributed to the study design. Contributed to outcome categorisation and data analysis. Reviewed and approved the manuscript. NS, EB, RB, HJ, NK, ES, DV, MW, TA-H, HN, JG: Contributed to the study design. Reviewed and approved the manuscript.

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APPENDIX

Supplementary file 1. List of all included studies

clinicaltrials.gov	
Trial registration number	**Trial title**
ACTRN12607000364471	Studies of Vitamin D supplements on Calcium Metabolism in Sarcoidosis
DRKS00000184	Influence of inhaled Aviptadil on the immunologic activity of alveolar macrophages in sarcoidosis
DRKS00011660	Safety and efficacy of Abatacept in patients with treatment-resistant sarcoidosis
EUCTR2007-005117-18-AT	Safety and efficacy study of bosentan in progressive pulmonary sarcoidosis - BOPSAC
IRCT2016081729405N1	Effects of 8 weeks of combined aerobic and resistive exercise on fat percentage, quality of life and fatigue in patients with pulmonary sarcoidosis
ISRCTN34533986	Antifungal medication improves treatment of sarcoidosis
ISRCTN73579020	BOSSA Study: Bosentan for the treatment of Steroid-resistant Pulmonary Sarcoidosis
NCT00001877	Treatment of Pulmonary Sarcoidosis With Pentoxifylline
NCT00073437	A Study of Infliximab in Patients With Sarcoidosis
NCT00262132	Mycophenolate for Pulmonary Sarcoidosis
NCT00279708	Atorvastatin to Treat Pulmonary Sarcoidosis
NCT00282438	Hematopoietic Stem Cell Support in Patients With Refractory Sarcoidosis
NCT00311246	Trial of Adalimumab in Progressive Sarcoidosis
NCT00361387	Use of Focalin for Fatigue in Sarcoidosis
NCT00555347	Use of Armodafinil for Fatigue in Sarcoidosis
NCT00701207	Study of Nicotine Patches in Patients With Sarcoidosis
NCT00739960	Safety Study of Abatacept to Treat Refractory Sarcoidosis
NCT00855205	Rituximab for Pulmonary Sarcoidosis
NCT00955279	A Study to Evaluate the Safety and Effectiveness of Ustekinumab or Golimumab Administered Subcutaneously (SC) in Patients With Sarcoidosis
NCT01732211	A Phase 2, Safety, Tolerability, and Efficacy Study of PD 0360324 in Chronic Pulmonary Sarcoidosis
NCT01830959	Use of Roflumilast to Prevent Exacerbations in Fibrotic Sarcoidosis Patients (REFS)
NCT01920919	Low-dose Dexamethasone in Newly Diagnosed Pulmonary Sarcoidosis
NCT02024555	Phase II Investigation of Antimycobacterial Therapy on Progressive, Pulmonary Sarcoidosis
NCT02155803	ACTHAR GEL for Sarcoidosis-Associated Calcium Dysregulation: An Open-label Pilot Study
NCT02188017	Acthar Gel for Chronic Pulmonary Sarcoidosis (ACPS)
NCT02200146	Hydroxychloroquine as Steroid-Sparing Agent in Pulmonary Sarcoidosis (HySSAS).
NCT02265874	Nicotine Treatment for Pulmonary Sarcoidosis: A Clinical Trial Pilot Study
NCT02523092	Use of CXCL9 as a Biomarker of Acthar Efficacy
NCT02888080	Study of Efficacy, Safety and Tolerability of ACZ885 (Canakinumab) in Patients With Pulmonary Sarcoidosis
NCT03260556	Pirfenidone for Progressive Fibrotic Sarcoidosis
NCT03265405	Efficacy and Safety of Two Glucocorticoid Regimens in the Treatment of Sarcoidosis
NCT03320070	Pilot Study to Assess the Efficacy and Safety of H.P. ActharÂ® Gel in Subjects With Pulmonary Sarcoidosis
NCT03621553	Vitamin D Homeostasis in Sarcoidosis
NCT03704610	Efficacy of Remission-induction Regimen With Infliximab for Severe Extrathoracic Sarcoidosis (EFIRTES)
NCT03727451	A Dose Escalation Study to Assess the Safety and Efficacy of Pulsed Inhaled Nitric Oxide in Subjects With Pulmonary Fibrosis or Sarcoidosis
NCT03824392	Study of Intravenous ATYR1923 for Pulmonary Sarcoidosis

Studies identified from qualitative literature	
1	Swayze, S. (1991). "Helping them cope." J Psychosoc Nurs Ment Health Serv 29(5): 35-37.
2	Victorson, D. E., D. Cella, H. Grund and M. A. Judson (2014). "A conceptual model of health-related quality of life in sarcoidosis." Quality of Life Research 23(1): 89-101.
3	Baughman, R. P., R. Barriuso, K. Beyer, J. Boyd, J. Hochreiter, C. Knoet, F. Martone, B. Quadder, J. Richardson, G. Spitzer, D. Valeyre and G. Ziosi (2018). "Sarcoidosis: patient treatment priorities." ERJ Open Research 4(4): 00141-02018.
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6	Voortman, M., C. M. R. Hendriks, M. D. P. Elferich, F. Bonella, J. Moller, J. De Vries, U. Costabel and M. Drent (2019). "The Burden of Sarcoidosis Symptoms from a Patient Perspective." Lung 197(2): 155-161.

PROMS (identified from the trials registered in clinicaltrials.gov) from which we extracted domains	
1	King's Sarcoidosis Questionnaire
2	Borg's CR10 dyspnea score
3	Fatigue Severity Scale
4	EuroQol - EQ5D
5	Leicester cough questionnaire
6	Saint George's Respiratory Questionnaire
7	Fatigue Assessment Scale
8	FACIT - Fatigue Scale
9	Sarcoidosis health questionnaire
10	SF-36