

# First patient-centred set of outcomes for pulmonary sarcoidosis: a multicentre initiative

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## ABSTRACT

**Introduction** Routine and international comparison of clinical outcomes enabling identification of best practices for patients with pulmonary sarcoidosis is lacking. The aim of this study was to develop a standard set of outcome measures for pulmonary sarcoidosis, using the value-based healthcare principles.

**Methods** Six expert clinics for interstitial lung diseases in four countries participated in a consensus-driven RAND-modified Delphi study. A mixed-method approach was applied for the identification of an outcome measures set and initial conditions for patients with pulmonary sarcoidosis. The expert team consisted of multidisciplinary professionals (n=14) from Cleveland Clinic, Cincinnati MC, Erasmus MC, Leuven UZ, Royal Brompton and St. Antonius Hospital. During a ranking process, participants were instructed to rank variables on a scale from 1 to 10 based on whether it has (1) impact of the outcome on quality of life, (2) impact of quality of care on the outcome and (3) the number of patients negatively affected by the outcome.

**Results** An outcome measures set was defined consisting of seven outcome measures: mortality, pulmonary function, soluble interleukin-2 receptor change as an activity biomarker, weight gain, quality of life, osteoporosis and clinical outcome status.

**Discussion** Collecting outcomes in pulmonary sarcoidosis internationally and the use of a broadly accepted set can enable international comparison. Differences in outcomes can potentially be used as a starting point for quality improvement initiatives.

## INTRODUCTION

Sarcoidosis is a chronic systemic disease of unknown aetiology, characterised histologically by granulomatous inflammation. Existing treatment options include either no medication or a mix of first-line, second-line and third-line medication with trade-offs between treating inflammation and quality of life (QoL).<sup>1</sup> A chronic disease course requires long-term treatment with corticosteroids, cytotoxics and other agents that can have a serious impact on the quality of life.<sup>2</sup> Significant grey areas exist in approaches

## Key messages

- This study provides detailed information on how the first set of patient-centred outcomes in patients with a diagnosis of pulmonary sarcoidosis was developed.
- The international process resulted in a consensus-driven recommended set.
- This standard set allows meaningful comparisons of outcomes and practices at different hospitals which can enable sharing of 'best practices' to improve the care for pulmonary sarcoidosis globally.

to treatment and thus how care is delivered across different countries and centres.<sup>3</sup> Little knowledge is available regarding outcomes of delivered care in relation to the various treatment options. Therefore, there is a need for standardisation of core outcomes to ensure high-value care delivery for all patients with sarcoidosis globally.

Patients suffering from chronic diseases have persistent needs and therefore need ongoing healthcare. Accordingly, patients with complex chronic conditions, such as sarcoidosis, are also the costliest patients, and costs increase with the number of chronic conditions.<sup>4</sup> In patients with sarcoidosis, it has been confirmed they have higher rates of comorbidity and complexity compared with a matched control group (matched for age and gender). Furthermore, it was found that the main comorbidities were pulmonary, liver, autoimmune and neoplastic disease in patients with sarcoidosis compared with controls.<sup>5</sup> It was estimated that commercial payers incurred US\$19 714 annually on healthcare costs spent per patient with sarcoidosis in the USA, with outpatient visits and inpatient admissions as the two main cost drivers.<sup>6</sup>



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Globally, healthcare providers are driven by similar goals: to improve patient experiences and healthcare outcomes, to become more efficient and to reduce the costs as well as to innovate the way care is provided. As addressed by Porter, value-based healthcare (VBHC) could be a guiding principle in achieving these multiple goals.<sup>7 8</sup> In particular, transparently sharing treatment outcomes of routine clinical care can help hospitals to learn from each other and improve patient value, defined as outcomes over costs.

Sarcoidosis often affects young and middle-aged adults. Patients suffer from a broad range of non-specific symptoms, with high variability in the degree of inflammation as well as organs affected. In more than 90% of the cases, sarcoidosis affects the lungs.<sup>2 9–11</sup> Spontaneous remissions occur in approximately two-thirds of the patients, but the disease course is chronic in 10%–30% of the patients.<sup>9</sup> Incidence and prevalence rates reported in the literature are highly variable. The prevalence varies over geographical regions as well as ethnic groups, with the highest sarcoidosis prevalence reported in the Nordic countries and in individuals of African descent.<sup>9 12</sup> For this study, we aimed to specifically develop a standard set of outcome measures for patients with pulmonary sarcoidosis.

In order to optimise treatment to the individual patient with sarcoidosis, the availability of centre-level outcome data has the potential to provide important advantages for quality improvement efforts. Hospitals can learn from variations in the outcomes of care, as demonstrated in cystic fibrosis centres.<sup>13</sup> Globally, there is a broader interest in studying the within-hospital as well as the between-hospital variation in various medical conditions.<sup>14 15</sup> Without having defined a set of meaningful and internationally accepted measures, it is not possible to compare results and identify best practices.

The primary objective of this study was to define a consensus-driven, patient-centred outcome set enabling international comparison of clinical outcomes of patients with pulmonary sarcoidosis, including a set of initial conditions needed for case-mix corrections.

## METHODS

### Study structure and design

A project group supervised the selection process of the outcome set. Initial identification of potentially relevant outcomes was established by an international working group with pulmonologists from six recognised expert clinics in four countries: Cleveland Clinic (USA), Cincinnati MC (USA), Erasmus MC (the Netherlands), Leuven UZ (Belgium), the Royal Brompton (UK) and the St. Antonius Hospital (the Netherlands).

An international team of experts (n=14) from the six expert clinics convened through webinars and a face-to-face session to reach consensus on the set of outcome measures and case-mix variables using a structured consensus-driven RAND-modified Delphi method (see online supplementary material appendix 1 for the full

list of experts).<sup>16 17</sup> The selection process was conducted between January 2014 and January 2015.

### Patient population and condition scope

The outcome set was designed for patients with pulmonary sarcoidosis. The working group acknowledged sarcoidosis as a very heterogeneous population, with the possibility of single extrapulmonary organ involvement, such as ocular sarcoidosis. However, as the lungs are involved in 90% of patients with sarcoidosis,<sup>2 18</sup> only patients with pulmonary involvement (including isolated hilar/mediastinal) were included in the dataset. The definition for sarcoidosis for this patient group was in line with the international accepted statement on sarcoidosis<sup>9</sup>: (1) the patient has to be diagnosed with pulmonary sarcoidosis and (2) the diagnosis is performed by a pulmonologist.

### Development of the standard set

In order to develop the standard set, a systematic approach was employed, identifying outcomes based on the three-tier principles of Porter: tier 1, health status (survival and degree of health); tier 2, recovery process (time to recovery, disutility of care); and tier 3, sustainability of health (ie, sustainability of health or recovery and long-term consequences of therapy).<sup>8</sup>

The development of the set was structured in three main phases. First, as introduced by Kaplan and Porter,<sup>8 19</sup> the care delivery value chain for pulmonary sarcoidosis was described. This allowed to map the total care delivery of the diverse activities. Second, a literature review was carried out by the working group guiding the identification of important outcomes and the related initial conditions. Third, the working group identified potential outcomes, applying the process for standard set development introduced by *Meetbaar Beter* (in 2017, *Meetbaar Beter* merged with the Netherlands Heart Registry).<sup>20 21</sup> The process described by *Meetbaar Beter* consists of the following steps: a list of the most important outcomes was sent to the expert group and prioritised. A structured consensus-driven, RAND-modified Delphi method was employed to prioritise the important outcomes anonymously on a scale from 0 to 10 (not important to most important). The outcomes were ranked on three criteria: (1) impact of the outcome on quality of life, (2) impact of quality of care on the outcome and (3) the number of patients negatively affected by the outcome. Based on the total score prioritising the outcomes, four online webinar discussions and one face-to-face meeting, final consensus on the outcome set was reached. A secondary goal of this process was to define a standard set of initial conditions required for potential case-mix corrections. This was defined based on expert opinion and was ranked accordingly. When differences in prioritisation emerged, they were openly discussed until consensus was reached.

**Table 1** Summary of standard set of outcomes for patients with pulmonary sarcoidosis

Outcome set	Category	Details	Timing	Data source
1. Mortality	Longitudinal outcomes	Date of death	Tracked throughout	Administrative
2. Pulmonary function	Clinical monitoring	1. FVC% predicted and absolute over treatment period 2. FEV <sub>1</sub> % predicted and absolute over treatment period 3. DLCO% predicted and absolute over treatment period	Every 3–6 months (depending on severity of sarcoidosis)	Clinical
3. Soluble interleukin-2 receptor (sIL-2R) change as an activity biomarker	Clinical monitoring	1. Date of measurement 2. sIL-2R (measured in pg/mL, limit >3000)	Every visit to the clinic	Clinical
4. Weight gain	Clinical monitoring	Weight (kg) measured at each pulmonary function test	Every visit to the clinic	Clinical
5. Quality of life; physical functioning	Patient-reported health status	King's Sarcoidosis Questionnaire <sup>40</sup> and the Fatigue Assessment Scale <sup>37</sup>	Every 6 months	Patient reported
6. Osteoporosis	Clinical monitoring	Diagnosis T-score 1=Normal >−1.0 2=Osteopenia <−1.0, >−2.5 3=Osteoporosis <−2.5 4=Severe osteoporosis <−2.5 plus fragility fractures 5=Not indicated <i>Based on WHO Osteoporosis Classification</i> <sup>52</sup>	Monitor throughout treating the patient	Clinical
7. Clinical outcome status <sup>41</sup>	Longitudinal outcomes	1=Resolved never treated 2=Resolved, no therapy >1 year 3=Minimal disease never treated 4=Minimal disease no therapy >1 year 5=Persistent no current therapy, never treated 6=Persistent no current therapy, no therapy >1 year 7=Persistent-current therapy, asymptomatic 8=Persistent-current therapy, symptomatic 9=Persistent-current therapy, worsening prior year 99=Unknown	After 2 years and/or 5 years	Clinician evaluation/administrative

## RESULTS

### Pulmonary sarcoidosis standard set

The care delivery value chain provides a detailed overview of care provided for patients with pulmonary sarcoidosis to guide the initial selection of outcome measures (see online supplementary material appendix 2 for a full description). After identifying the most important outcomes from the care delivery chain, literature and expert opinion, an initial set of 34 outcomes was presented to the expert group (see online supplementary appendix 4). Next, outcome measures were ranked based on the *Meetsbaar Beter* criteria delineated earlier.<sup>20,21</sup> Finally, the ranking and expert opinion discussions resulted in seven outcome measures (table 1) and 10 initial conditions (table 2). Further information how the outcomes were prioritised is presented in the online supplementary material appendix 4. An overview of data collection and its timeline is presented in figure 1.

In the following paragraphs, we discuss our considerations in selecting the seven outcome measures in relation to the literature. For more detailed information concerning the outcome measures, please see online supplementary appendix 3 in the online supplement.

### Tier 1: outcome measures 1, 2 and 3: health status (survival and degree of health)

Survival at 1 and 5 years after the diagnosis is an important outcome (*outcome measure 1*), especially for patients with advanced pulmonary sarcoidosis. Survival is measured as all-cause mortality, calculated from clinical and administrative data sources. Sarcoidosis-related mortality is reported to be up to 7.6% in a US-based population.<sup>22</sup> Most deaths are due to pulmonary fibrosis, pulmonary hypertension, neurological and cardiac involvement.<sup>9</sup>

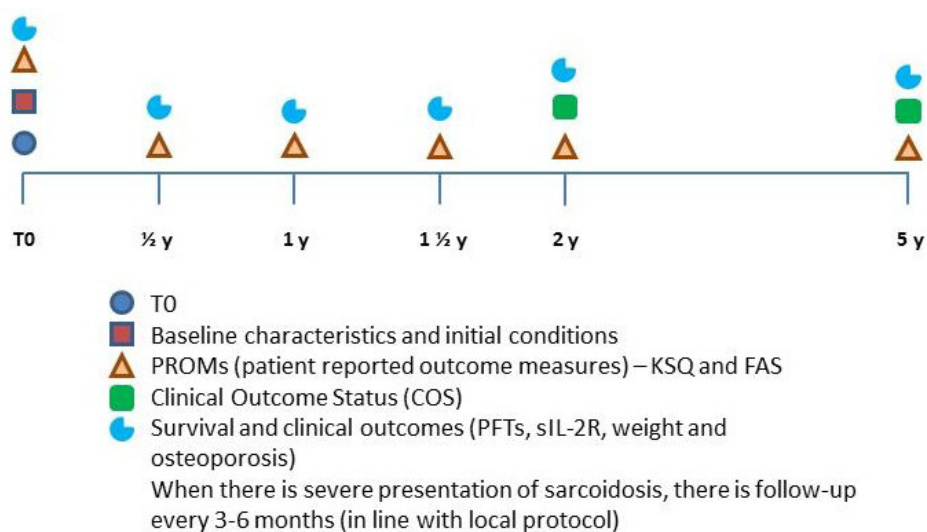
*Outcome measure 2* is pulmonary function (FVC, FEV<sub>1</sub> and DLCO), which is widely used to monitor disease

**Table 2** Summary of standard set of initial conditions for patients with pulmonary sarcoidosis

Timing for collection	Measure	Details	Source
First contact with hospital services	Age	Date of birth	Administrative
At time of clinical visit	Body mass index	Weight and height needed	Clinical
At time of clinical visit	Comorbidity ICD-10+sleep apnoea	Documented in history	Clinical
First contact with hospital services	Ethnicity	Documented in history	Administrative
First contact with hospital services	Gender	Gender at birth Documented in history	Administrative
At time of clinical visit	Multiorgan involvement <sup>53</sup>	Various clinical manifestations for the probability of various sarcoidosis-related organ involvement. Ranking options are highly probable, at least probable, possible or no consensus	Clinical
First contact with hospital services	Opinion stage (first, second, third)	1. First opinion 2. Second opinion 3. Third opinion	Clinical
Stadium X-thorax <sup>42</sup>	Scadding stage based on chest X-ray	1. Stage 0: normal 2. Stage I: lymph nodes in hili or mediastinum 3. Stage II and III: I plus distortion in lung (II) 4. Stage IV: fibrosis in lung, significant fibrotic lesions/end-stage disease	Clinician evaluation/ administrative
First contact with hospital services	Smoking history	1. Never 2. Ever 3. Active (moment of diagnosis an active smoker)	Administrative
First contact with hospital services	Socioeconomic status	Postal code	Administrative

progression. Currently, serial FVC is considered as the best endpoint to monitor during the course of care for pulmonary sarcoidosis.<sup>23</sup>

Finally, soluble interleukin-2 receptor (sIL-2R) was selected as outcome measure 3. sIL-2R is considered to be a marker of T-cell activation.<sup>24</sup> A shortcoming of



**Figure 1** Example of a timeline when outcomes and baseline factors should be collected for patients with pulmonary sarcoidosis. This timeline represents the outcome data collection points for a possible treatment path of a patient with pulmonary sarcoidosis. It does not advocate a particular treatment or treatment combination. Patients can receive follow-up for up to 5 years, but this can also be longer depending on the disease severity and whether the patient experiences chronic pulmonary sarcoidosis. T0=at first physician visit. FAS, Fatigue Assessment Scale; KSQ, King's Sarcoidosis Questionnaire.



this outcome is the fact that it is not routinely measured and implemented in all the collaborating expert clinics. Furthermore, there are conflicting data regarding the correlation between sIL-2R level changes and respective treatment response.<sup>25</sup> However, it outperforms conventional biomarkers such as ACE<sup>26</sup> and is cheaper and more widely available than sensitive tests like fluorodeoxyglucose PET.<sup>27</sup>

### Tier 2: outcome measure 4: recovery process (time to recovery, disutility of care)

The treatment of pulmonary sarcoidosis aims at preventing a progressive disease pattern with organ failure. The clinical manifestations are widely variable, ranging from asymptomatic radiographic findings to a more chronic progressive disease pattern with multiple organ failure.<sup>28</sup> However, complications due to the treatment of pulmonary sarcoidosis are also significant, such as adverse side effects due to high-dose and/or long-term prednisone use, excessive weight gain, risk of osteoporosis and fatigue.<sup>29–31</sup> Globally, corticosteroids, such as prednisone, remain the mainstay of therapy in sarcoidosis.<sup>9,32</sup> The initial recommended dose of prednisone is 20–40 mg/day, which should later be tapered down to a dose around or below the 10 mg/day.<sup>33</sup> However, it remains debated whether prednisone therapy modifies long-term progression of the disease.<sup>34</sup> We chose weight gain as a measure of disutility of care, *outcome measure 4* in the outcome measures set.

### Tier 3: outcome measures 5, 6 and 7: sustainability of health (ie, sustainability of health of or recovery and long-term consequences of therapy)

Health-related quality of life (HRQOL), a key measure for patients with pulmonary sarcoidosis, is *outcome measure 5*. Fatigue is the most common complaint in patients with pulmonary sarcoidosis, reported by 50% to 80% of patients.<sup>35,36</sup> The process aims to select well-validated instruments to address the multidimensional outcome domains, minimising the burden for the patients (eg, number of questionnaires/questions to fill out) on the one hand, while maximising the likelihood of solid longitudinal data collection on the other hand. The Fatigue Assessment Scale (FAS) and King's Sarcoidosis Questionnaire (KSQ) were selected as the most appropriate patient-reported outcome measures in order to monitor changes in patients' quality of life (online supplementary material appendix 5 and appendix 6). The FAS is a well-defined and validated questionnaire in patients with sarcoidosis.<sup>23,37</sup> The cut-off score for presence of fatigue is >21 points.<sup>23</sup> The minimal clinically important difference is defined at a 10% reduction or a change of four points.<sup>38</sup> The KSQ is a self-administered measure for sarcoidosis covering five different domains of health status: (1) general health status, (2) lung, (3) medication, (4) skin and (5) eyes.<sup>39</sup> It consists of 29 questions. The KSQ is available in multiple languages.<sup>39,40</sup>

Patients with pulmonary sarcoidosis are at risk for developing osteoporosis for a number of reasons, including corticosteroid treatment and reduced mobility secondary to lung function impairment/musculoskeletal issues or other internal organ involvement such as the heart. Data on osteoporosis development were therefore included as *outcome measure 6* of the set.

The WASOG Task Force recommends to score patients based on nine predefined criteria, 2 and/or 5 years after diagnosis, introduced as the clinical outcome status (COS).<sup>41</sup> The COS is defined as *outcome measure 7* of the set. The aim of applying the COS is to standardise the clinical outcome description of patients with sarcoidosis and can be seen as an important tool for treatment related classification. For example, patients with persistent disease still on therapy at time of repeat evaluation are COS 7, 8 or 9.

### Initial conditions

A minimum set of initial conditions to control outcomes for differences in patient characteristics was defined. This includes characteristics of pulmonary classification on a chest radiograph into five stages (Scadding stage).<sup>42</sup> Also, general patient demographics (age, sex, first, second-opinion or third-opinion stage, race/ethnicity, body mass index, comorbidities) and treatment-related factors are included. These initial conditions are associated with the disease outcomes ([table 2](#)).

The included comorbidities are based on the ICD-10 codes plus the addition of sleep apnoea (online supplementary appendix 3). This was determined by the treating physician and entered into the patient's medical record. For pulmonary sarcoidosis, the ability to identify black/African-American patients is important, as the disease was found to be more severe in black patients.<sup>43</sup> Race/ethnicity documentation however differs by country, as well as the means to capture the information (self-reported; Caucasian or non-Caucasian vs Hispanic or non-Hispanic). For more detailed information concerning the initial conditions, please see online supplementary appendix 3. The initial conditions were extracted from the patient's administrative and clinical data (such as Scadding stage, history of diabetes mellitus or sleep apnoea) and were collected when the patient visits the clinic for the first time ([table 2](#)).

### Medication use

In addition to the outcome set and the case-mix variables, we also decided to collect information concerning the patients' medication at diagnosis and at the time of each visit to the clinic. We aimed to identify the duration and variation of first-line, second-line and third-line therapy and to allow comparison between centres. In addition, in relation to weight changes, the team of experts thought medication differences could provide meaningful information to better explain weight changes due to prednisone use. Corticosteroid therapy have been reported to lead to significant changes in HRQOL.<sup>44</sup> Even low

doses of prednisone have been associated with significant morbidity.<sup>30 31</sup> Although this was not part of the outcome measures set, consensus was reached to monitor the following drugs: corticosteroids, methotrexate, azathioprine, non-steroidal anti-inflammatory drugs, infliximab, adalimumab, other anti-TNF, leflunomide, inhalation therapy, other systematic therapy for (extra)pulmonary sarcoidosis and hydroxychloroquine.

## DISCUSSION

A first outcome measure set was developed for patients with pulmonary sarcoidosis consisting of seven outcome measures: mortality (1 and 5 years), pulmonary function (FEV<sub>1</sub>, FVC, DLCO<sub>c</sub>), sIL-2R change as an activity biomarker, weight gain, quality of life, osteoporosis and clinical outcome status. Routine data collection based on standardised outcome measures creates an opportunity to improve patient care. A reliable data collection process for patients with pulmonary sarcoidosis enables us to compare outcomes between various clinics/treatments, which can ultimately help to identify best practices.

The international consensus process resulted in a set of patient-centred outcomes with case-mix variables. This can enable clinicians to measure and benchmark outcomes. It is, however, important to note that the set presented in our paper should not limit any inclusion of additional treatment and/or process-related outcomes supporting quality improvement efforts. It is expected that in efforts to create a multicentre registry, centres will continue to collect additional data, such as the initial dose of prednisone, the rate of prednisone tapering and the timing of a potential switch to second-line therapy (such as methotrexate or azathioprine).

This outcome measures set could be used on a monthly or yearly basis in order to benchmark outcomes. Moreover, this set can be used to compare the quality of care delivered by different centres around the world, which in turn can trigger discussion and define future learning potential for other clinics treating this patient group. Second, it could be used to assess best practices in a field where there is a scarcity on evidence-based therapies. Other initiatives have developed classification protocols, although this is more based on clinical criteria as a tool for studies evaluating disease mechanisms in patients with sarcoidosis to be correlated with clinical outcomes.<sup>45</sup> For example, the GRADS initiative aims to compare blood genomics with clinical phenotypic variables and assess each participant's clinical course during follow-up.<sup>46</sup> This recommended outcome measures set is a first step at applying a global standard. Future experiences in comparing outcomes using the set are needed to further refine the global standard set.

Ultimately, healthcare-related patient value should be defined as value achieved from the perspective of the patient and their respective changes in most important clinical outcomes relative to its costs.<sup>8</sup> This includes perceived health status, QoL as well the impact of choices

made during treatment, for example, weight gain as a side effect due to prednisone. The establishment of an international global standard to collect and compare outcomes for patients with pulmonary sarcoidosis will enable more systematic follow-up of the patients' quality of life.

In order to support further progress to measure and transparently compare outcomes for pulmonary sarcoidosis, investments should be made in a longitudinal-oriented registry. This will result in a more structured process when collecting this type of outcome data. In addition, improving the data infrastructure and relying on less manual data entry can improve the validity of the data.

The ultimate goal when reporting clinical outcomes is to inform patients, clinicians and managers with credible performance data.<sup>47</sup> Additionally, improved documentation, open communication, encouraging quality improvement and increasing informed decision-making for patients are of great importance when reporting and comparing outcomes.<sup>48</sup> Making use of a clinical registry and reporting outcome data through, for example, annual reports to the public can promote quality improvements in healthcare, reduce potential variations in the quality of care delivered and improve data validity.<sup>49 50</sup>

The set was developed by physicians, as there was a strong need for standardisation from the medical specialties. Annual maintenance cycles in order to evaluate the set should be considered important to continuously improve the set, as suggested by others.<sup>21</sup> These cycles can be used to generate new scientific input to re-evaluate the outcome measures incorporated in the set.

The interdisciplinary character can be improved (eg, include radiologist and psychologist in the expert group during maintenance cycles). Also, five out of the 14 expert group members were affiliated with the St. Antonius Hospital. This was due to the fact that this centre initiated the study. Although this can create potential bias, during the webinars consensus was reached among all expert group members. In addition, it is necessary to discuss and validate the set with patients and possibly further improve the set using their perspectives as we did not include patient perspectives in the generation of the consensus. In a recent study (in press), survey findings showed that patients (n=1842) want quality of life and functionality to be included as outcomes in their treatment.<sup>51</sup> In this study, patients from different countries were included (692 Dutch, 528 German, 338 English, 148 Italian, 107 Spanish, 29 French). Finally, for the development of this set, we had an international group with experts from different centres, but not all continents were represented. Future efforts on updating the outcome set should put more efforts on a larger global coverage and collaboration between different centres treating patients with pulmonary sarcoidosis.

## CONCLUSIONS

The international process resulted in a consensus-driven recommended first set of patient-centred outcomes in patients with a diagnosis of pulmonary sarcoidosis. Applying this outcome set has the potential to better inform patients, healthcare providers and other stakeholders in achieving value-based care for patients with pulmonary sarcoidosis. The full potential of applying VBHC principles in pulmonary sarcoidosis is however yet to be explored.

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