

VALUE-BASED HEALTHCARE IN PULMONARY SARCOIDOSIS

PAVING THE WAY FOR A NEW APPROACH



A. Nynke Kampstra

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ANTJE NYNKE KAMPSTRA

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VALUE-BASED HEALTHCARE IN PULMONARY SARCOIDOSIS PAVING THE WAY FOR A NEW APPROACH

Waardegedreven zorg in pulmonale sarcoïdose
de weg naar een nieuwe aanpak
(met een samenvatting in het Nederlands)

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"Let the dataset change your mindset."

- Prof. dr. Hans Rosling -

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Introduction and Outline of the Thesis



INTRODUCTION

The aim of this thesis is to investigate whether value-based healthcare (VBHC) can be of use for developing care for patients with pulmonary sarcoidosis. Little knowledge is available on applying the concept of VBHC in specific patient groups and whether this can be meaningful, add value and improve outcomes. Improving the quality of care is an overall goal for all diseases, including rare diseases such as pulmonary sarcoidosis. However, with little data coming from randomized controlled trials (RCTs) and longitudinal data collections, improving clinical outcomes based on scientific evidence is difficult. This results in the fact that many grey areas exist in day-to-day healthcare delivery. Globally, there is extensive variation in the management of patients with pulmonary sarcoidosis. Bringing together experience and expertise in a structured manner and comparing results across centers around the world, as is the essence of VBHC, might help improve diagnostics and treatment practices, especially in rare diseases. Consensus on a standard set might be a valuable addition, reaching more standardization on the most important outcome measures for patients with pulmonary sarcoidosis, and advancing development of care. This thesis therefore focuses on developing, implementing and evaluating a standard set of patient-relevant outcome measures for patients with pulmonary sarcoidosis.

This chapter introduces the VBHC concept and the potential of applying VBHC in patients with pulmonary sarcoidosis. Furthermore, it provides an overview of developments in the field of quality improvement. Finally, it presents the objectives and the outline of this thesis.

VALUE-BASED HEALTHCARE

Value, according to Michael Porter in 2006 and later described in more detail in 2010, is defined as the health outcomes achieved relative to the expenses needed to come to the particular outcome(s) ($\text{value} = \text{outcomes} / \text{cost}$).^[1] The concept was developed to (re)define the shared goal in healthcare uniting the various stakeholders' interests and activities.

In order to measure value, the outcomes (the numerator in the 'value equation') as part of the set should be condition-specific and multidimensional. In addition, the outcome measures together should cover outcomes the patient considers important during the different phases of care they underwent. In order to cover the most important both short-term and long-term outcomes, three tiers have been designed to encompass the results of care (Figure 1).^[1]

In 2012, the International Consortium for Health Outcomes Measurement (ICHO), aiming to standardize the development of standard outcome sets, was founded.[2] As of July 2021, ICHO has developed 40 standard outcome sets using a structured process.[3] Four standard outcome sets are in progress. In various patient groups, also outside of ICHO's initiatives, outcome sets have been defined.[4–8] In addition, the Outcome Measures in Rheumatoid Arthritis Clinical Trials initiative (OMERACT) currently consists of over 40 working groups and has defined various outcome measures sets (core sets) for diseases such as fibromyalgia and rheumatoid arthritis.[9, 10] However, to date no outcome set had been defined for patients with pulmonary sarcoidosis.

VBHC has been translated into the contexts of international, national and regional healthcare systems. Multiple discourses have been found in how a stakeholder or organization defines VBHC and how they aim for more value for patients.[11] Nowadays, VBHC is more than only developing standard sets after a decade of research. Moreover, a strategic agenda for value transformation has been described consisting of six elements. [12] The six elements of this agenda are:

1. organize into Integrated Practice Units (IPUs);
2. measure outcomes and costs for every patient;
3. move to bundled payments for care cycles;
4. integrate care delivery systems;
5. expand geographic reach;
6. build an enabling information technology platform.

In addition, based on implementation experience in the last decade, it was suggested this strategic agenda should be extended with four elements.[13]:

1. set up value-based quality improvement;
2. integrate value in patient communication;
3. invest in a culture of value delivery (education);
4. Build learning platforms for healthcare professionals.

In addition, a strategic framework guiding organizations in applying value-based healthcare implementation was described.[14]

As a conceptual framework, the application of VBHC can still be seen as an emerging topic. Experiences with value-based healthcare in a scientific context are limited.[15, 16] Outcomes resulting from day-to-day healthcare delivery and its costs are often unknown, also for patients with pulmonary sarcoidosis. Specifically, as there is no international

consensus on important clinical and patient-reported outcomes for patients with pulmonary sarcoidosis, developing a patient-centered set of outcomes was the first step in this thesis.

MEASURING OUTCOMES

Nowadays many hospitals have started tracking outcomes across the continuum of care. [2, 17] To stimulate this development by healthcare professionals, patients and healthcare providers, the Dutch Ministry of Health, Welfare and Sport in the Netherlands invested €70 million in the program *“Uitkomstgerichte zorg”* (2018-2022).[18] The availability of data on outcome measures is considered a key ingredient for being able to realize quality improvement.

In a recent study among 197 residents in the Netherlands it was concluded that residents prefer knowledge on both medical practice as well as on themes related to the process of care. [19] They furthermore concluded residents would like to be educated on VBHC (by an expert) together with a clinician and that there is inclusion of VBHC in their educational plans. The leading American national physician association (the American College of Physicians) states that medical institutions are responsible to address VBHC and has therefore developed curricula to stimulate VBHC.[20] In a survey amongst 394 physicians in the United States, only 27% believed that quality measures were moderately or strongly representative of measuring and capturing the quality of care.[21]

When outcome sets are developed for a specific patient group, they should be measurable. In addition, it should also be feasible to measure the outcomes. Feasibility in this context is defined as “the extent to which the required data are readily available or could be captured without undue burden and can be implemented for performance measurement”.[19]

Little is known about the actual (inter)national application of the standard sets in daily clinical practice. Can the outcome measure be collected in the majority of the patients? One study has proven it is feasible to measure a comprehensive set of patient-relevant outcome measures for patients with coronary artery disease.[6] The set was implemented in 21 Dutch hospitals in order to improve cardiac care. They furthermore indicated that the variation of the results among the centers provide sufficient opportunities to improve cardiac care in the Netherlands.

Another study evaluated the feasibility and alignment of two international standard outcome sets in a multicenter setting for cataract surgery and macular degeneration.[22] They evaluated the consistency of ophthalmic outcome measures reported within eight hospitals. They concluded that globally the reported outcomes for ophthalmic conditions widely vary across hospitals. However, they did not include patient-reported outcomes.

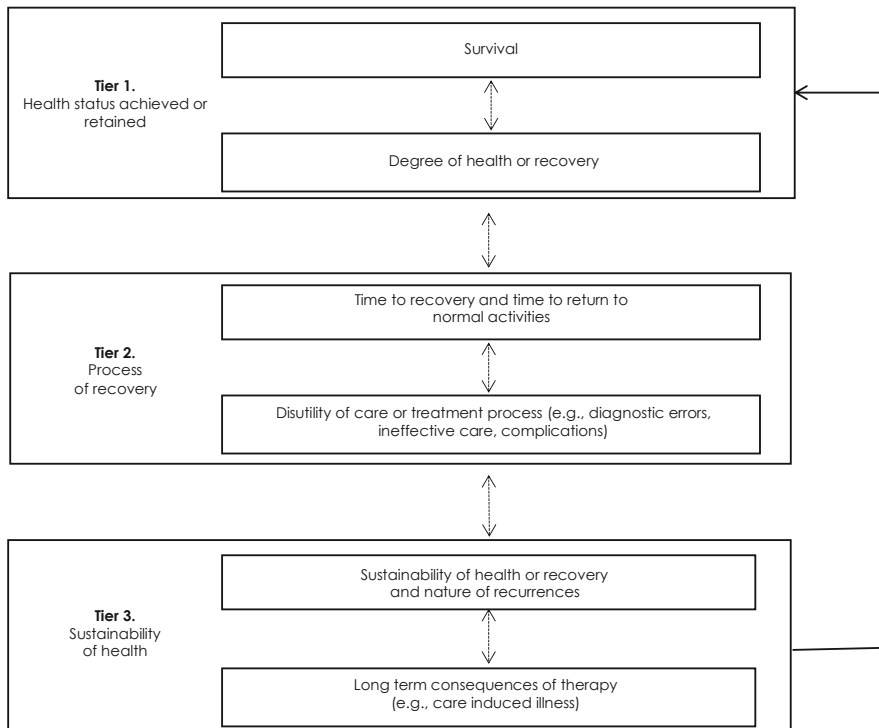


Figure 1. The Outcome Measures Hierarchy [1]

COSTS AND HEALTHCARE UTILIZATION

Globally, healthcare providers are faced with rising costs due to expensive treatments and aging populations.[23] The Netherlands spent about 10% percent of its gross domestic product (GDP) to healthcare in 2019 and 2020.[24] OECD countries on average spend 28% of their total healthcare expenses on hospital inpatient care.

In response to the increasing costs, it becomes more important to be transparent regarding underlying service costs and cost drivers. This transparency can then be used to identify low value and wasteful services. According to Porter, costs are the sum of total costs of the

full cycle of care for the patients with a particular disease.[1] In the scientific community and clinical practice, there is little consensus on how to measure costs. It is considered important that besides outcome data, cost data are also readily available and accessible. [25] However, it remains difficult to trace and measure costs. In the Netherlands, the hospital collects all costs related to the hospital visits and treatment. This is all pulled together in one bill: the diagnosis-treatment combination (DBC). The price of a DBC is based on the costs of an average treatment. This allows the medical staff to adapt the care to each situation without first having to negotiate the costs with the insurer. The DBC also includes costs that are not directly related to the treatment. Thus, in the Dutch reimbursement system it is difficult to measure and collect the real costs.

For patients with (pulmonary) sarcoidosis, few studies have evaluated costs. One study showed median yearly healthcare costs for patients with sarcoidosis in a US-based population are \$18,663 per year.[26] In that same population, the median costs for the top 5% were however much higher, \$93,201 per year. In a 12-month follow-up period it was shown that 20% of the high-cost patients accounted for 72% of the total healthcare expenditures.[27] However, little is known about the healthcare utilization and patient characteristics in high-cost patients with sarcoidosis. No other studies have tried to identify cost-drivers in high-cost patients with sarcoidosis. This can be valuable as it will enable to assess the effectiveness of current treatment choices.

PULMONARY SARCOIDOSIS

In this thesis, we apply VBHC in patients with pulmonary sarcoidosis. Sarcoidosis is a multi-systemic disease characterized by the formation of granulomas in diverse organs. In Northern European countries, up to 40 sarcoidosis cases per 100,000 people have been reported.[28] In the Netherlands there are approximately 7,500 patients with sarcoidosis. The prevalence is variable comparing different geographical regions and ethnic groups, with the highest sarcoidosis prevalence reported in the Nordic countries and in African-Americans.[29] Sweden has a prevalence of 160 per 100 000 inhabitants. Moreover, the incidence of sarcoidosis studied during the period 2003–2012 in Sweden was 11.5 per 100.000 people per year.[26, 27] In African Americans this is 36 cases per 100,000 people per year.[29]

The disease involves the lungs and thoracic lymph nodes in approximately 90% of the patients.[29, 31] Severe fatigue is one of the most common complaints in this patient group.[32, 33] No cure exists and treatment aims mostly at symptom relief and suppression of inflammation. The clinical course of sarcoidosis is highly variable, ranging from self-

limiting to a chronic disease course (in 10-30% of the cases).[29] In a US-based population, mortality is reported to be up to 7.6%.[30] Most deaths are due to pulmonary fibrosis, neurologic and cardiac involvement.[29]

Many grey areas exist in the treatment and pharmacological management for patients with pulmonary sarcoidosis. In order to optimize treatment, the availability of center-level outcome data has the potential to provide important advantages for quality improvement efforts.

Value-based healthcare in pulmonary sarcoidosis

Measuring the quality of care is of great importance, especially in a disease such as pulmonary sarcoidosis, where a paucity of data coming from RCTs exists. If hospitals were more transparent and shared treatment outcomes of routine clinical care, hospitals may potentially learn from each other and identify differences in daily clinical practice. Especially for rare diseases and due to its small patient populations to learn from, centers may bring together their experience and expertise. When evaluating a large and multicenter patient cohort, it will be possible to gain more insight after which healthcare professionals can potentially improve diagnostics and treatment practices. Currently, little consensus exists on what the most important outcome measures are concerning the daily clinical practice for patients with pulmonary sarcoidosis.[34] Although VBHC has shown to be of value in other chronic diseases such as inflammatory bowel disease,[35] applying VBHC in an orphan (and in some patients chronic) disease remains unknown. Consensus on a standard set might be a valuable addition reaching more standardization on the most important outcome measures for patients with pulmonary sarcoidosis.

VBHC AT THE ST. ANTONIUS HOSPITAL

In 2010, VBHC became part of the St. Antonius hospitals' strategy. Nowadays, for 22 disease areas improvement initiatives exist.[36] At the St. Antonius hospital a continuous improvement cycle is being used to realize improvements. Improvement cycles run over a six-month period, consisting of three major phases: (1) data collection and analysis, (2) the identification of improvement opportunities, and (3) the implementation of improvement projects.

In 2015, funding was received in order to start a VBHC project within the internationally renowned Interstitial Lung Diseases (ILD) Center of Excellence, specifically for patients with pulmonary sarcoidosis.[37] Sarcoidosis patients represent about 40% of the ILD patients, of which 90% show pulmonary involvement.[29]

The Santeon group is a collaborative of seven non-academic teaching hospitals in the Netherlands and was founded in 2007.[38] The St. Antonius hospital is one of the seven Santeon hospitals. Nowadays, the Santeon hospitals closely work together on 15 patient groups/ disease areas.[39] Their aim is to continuously improve healthcare through innovation and to collect outcomes in order to learn from each other. Santeon's VBHC initiative was launched in 2012.[36]

AIM OF THESIS

The overall aim of this thesis is to implement and evaluate the standard set for patients with pulmonary sarcoidosis in a multicenter-setting. It is furthermore investigated if and how measurement of outcomes in the standard set can be used as a strategy to improve health outcomes. Finally, healthcare resource utilization and costs are presented. For this, the following research questions were formulated:

1. What outcomes and measures should be part of a patient-centered standard set of outcome measures for patients with pulmonary sarcoidosis in a multicenter setting?
2. How can outcome measures from clinical registries help to implement and monitor quality improvement initiatives? What are facilitators and/or barriers that contribute to the realization of QI efforts?
3. What is the feasibility to use the set of outcome measures for patients with pulmonary sarcoidosis in a multicenter setting?
4. When applying VBHC-principles, what is a best practice for patients with pulmonary sarcoidosis and how did this best practice affect outcomes?
5. What are utilization patterns and healthcare costs in patients with sarcoidosis?

OUTLINE OF THESIS

This thesis is subdivided into three parts. In Part I, the added value of measuring health outcomes is discussed. In Part II, a patient-centered set of outcomes for patients with pulmonary sarcoidosis is presented. Moreover, it presents the results of the outcome indicator set for pulmonary sarcoidosis, measured in a multicenter setting. Finally in Part III, the implementation of a best practice is evaluated. In addition, healthcare resource utilization and costs in patients with sarcoidosis are presented.

Part I *Health outcome measurement and quality improvement*

- **Chapter 2** provides an overview of how health outcome measurement and organizational readiness can support quality improvement.

Part II*Development and evaluation of the outcome indicator set for pulmonary sarcoidosis*

- **Chapter 3** describes a patient-centered set of outcomes for patients with pulmonary sarcoidosis developed and how this was developed in a multicenter setting.
- **Chapter 4** presents the results of the outcome indicator set for pulmonary sarcoidosis and its feasibility.

Part III *Implementation of best practice & costs*

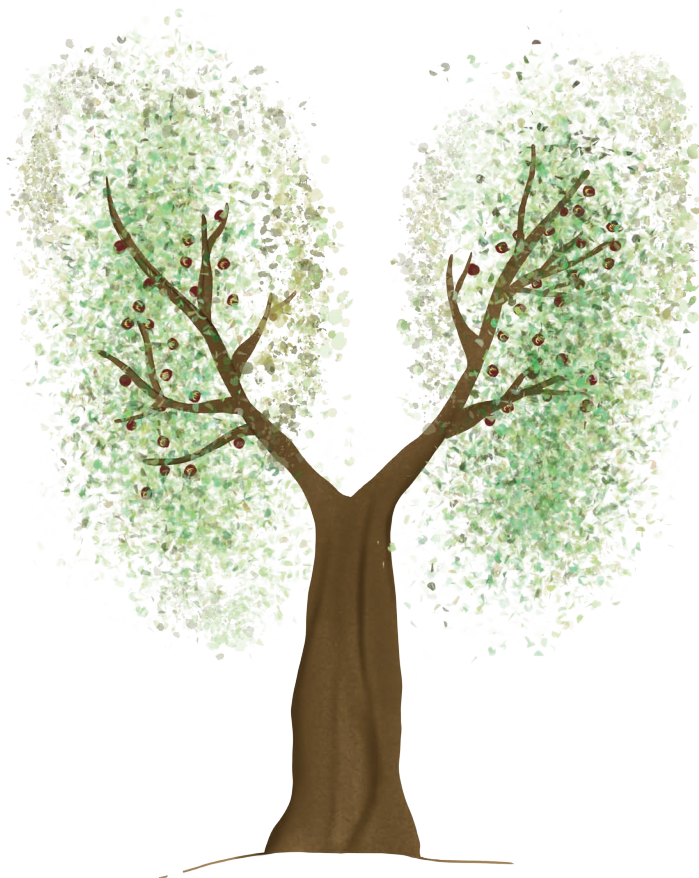
- **Chapter 5** presents data on patterns of healthcare resource utilization and costs in patients with sarcoidosis with and without fatigue related symptoms.
- **Chapter 6** presents a newly implemented prednisone protocol in pulmonary sarcoidosis patients. Also, impact of the new protocol on outcome measures as part of a before-after comparison is presented.

Finally, **Chapter 7** provides a general discussion with a reflection on the results of this thesis and presents concluding remarks.

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Health Outcome
Measurement and
Quality Improvement

Part





Health Outcomes
Measurement and
Organizational
Readiness Support
Quality Improvement:
a Systematic Review

2

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ABSTRACT

Background: Using outcome measures to advance healthcare continues to be of widespread interest. The goal is to summarize the results of studies which use outcome measures from clinical registries to implement and monitor QI initiatives. The second objective is to identify a) facilitators and/or barriers that contribute to the realization of QI efforts, and b) how outcomes are being used as a catalyst to change outcomes over time.

Methods: We searched the PubMed, EMBASE and Cochrane databases for relevant articles published between January 1995 and March 2017. We used a standardized data abstraction form. Studies were included when the following three criteria were fulfilled: 1) they relied on structural data collection, 2) when a structural and comprehensive QI intervention had been implemented and evaluated, and 3) impact on improving clinical and/or patient-reported outcomes was described. Data on QI strategies, QI initiatives and the impact on outcomes was extracted using standardized assessment tools.

Results: We included 21 articles, of which eight showed statistically significant improvements on outcomes using data from clinical registries. Out of these eight studies, the Chronic Care Model, IT application as feedback, benchmarking and the Collaborative Care Model were used as QI methods. Encouraging trends in realizing improved outcomes through QI initiatives were observed, ranging from improving teamwork, implementation of clinical guidelines, implementation of physician alerts and development of a decision support system. Facilitators for implementing QI initiatives included a high quality database, audits, frequent reporting and feedback, patient involvement, communication, standardization, engagement, and leadership.

Conclusion: This review suggests that outcomes collected in clinical registries are supportive to realize QI initiatives. Organizational readiness and an active approach are key in achieving improved outcomes.

INTRODUCTION

The use of clinical registries is considered crucial to systematically measure clinical outcomes in achieving better value for patients [1]. A clinical or patient registry is defined as "an organized system that uses observational study methods to collect uniform data (clinical data as structure, process and outcome measures) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure" [2]. Registries that are used for evaluating patient outcomes are used for the purpose of this review. The importance of clinical registries has been widely recognized as a tool to realize quality improvement (QI) and public accountability [1,3–8]. Medical associations use clinical registries for collecting data using pre-defined measures in patients undergoing a certain procedure or for a specific disease [9]. In particular, feedback based on clinical registry data is used to identify and monitor improvement initiatives [10]. Therefore, registries are seen as a promising tool to achieve improvements in value for the patient by measuring outcomes [1]. A previous review on the structure, use and limitations of current clinical registries showed that registries and their respective measures are used for monitoring providers, discussion platforms for QI, improving risk adjustment modelling and for improving preoperative risk profiling [11]. However, the current body of literature lacks insights into the extent to which the use of outcome measures from clinical registries, either when identifying, selecting or monitoring QI initiatives, can impact health outcomes.

With rising healthcare costs, service restrictions, differences in quality and costs, there is an increasing need for reform to improve value of healthcare [12]. Value in healthcare is defined as outcomes relative to costs [13]. Value-based healthcare aims at achieving higher value for patients while ensuring sustainability of the healthcare system by an efficient and effective delivery of care [14]. This goal is assumed to be achieved by measuring and using outcomes per medical condition for the identification of improvement potential across the full cycle of care [12]. Higher value for patients by measuring outcomes is one of the potential methods for improving quality of healthcare relative to the costs spent. For the purposes of this review, we only focused on outcome measures and not on the respective costs.

Quality of healthcare is generally assessed by using structure, process or outcome measures [15]. The latter provide insights into outcomes of a certain disease or several diseases, for instance on survival, functional status, and quality of life [16]. The aim of measuring outcomes is diverse; guiding clinical decision-making, initiating improvement interventions, benchmarking, monitoring, scientific research and public accountability. Measuring outcomes structurally and using them to identify possible improvements contributes to the aim of achieving higher value for patients [17].

The goal is to summarize the results of studies which use outcome measures from clinical registries to implement and monitor QI initiatives. For the purposes of this study, QI was defined as the application of a defined improvement process to achieve measurable improvement by implementing an improvement intervention. Registry data itself is not sufficient as they need QI methods in order to achieve actual improvement. The second objective is to identify a) facilitators and/or barriers that contribute to the realization of QI efforts, and b) how outcomes are being used as a catalyst to change outcomes over time.

METHODS

A systematic review was conducted of studies published between January 1995 and March 2017. The search strategy was designed for PubMed, EMBASE and Cochrane databases. To identify evidence for the use of clinical registries to improve or contribute to patient health outcomes, the following PubMed Mesh terms were used to identify studies: *mortality*, *patient outcome assessment* and *treatment outcome*. These terms were combined with a variety of search terms related to QI and diverse disease specific registry studies. No specific patient group or study design was defined. Details of the complete search strategy are provided in appendix 1. Additional hand-searching has been conducted for systematic reviews on the subject during the review process. The hand-search was conducted in Google Scholar.

Inclusion and exclusion criteria

Studies were included when they met each of the following criteria: 1) published in peer-reviewed journals, 2) published in English, French or German, 3) the study actively implemented a strategy using outcome data to realize QI, 4) the study relied on structural data collection, and 5) the study evaluated the QI interventions realized. Whether a study made use of a QI effort, falling under criteria 3 and 5, was evaluated after reviewing the full text papers and was therefore not part of the search string. After title screening, included studies were evaluated on criteria 3 and 5. Studies were excluded when they analyzed the effect of new intervention(s) on outcomes (testing drugs, new techniques or the effect of an intervention) or when the data had solely been collected to evaluate an intervention in a clinical trial.

Data extraction and quality assessment

For the initial selection each reviewer reviewed a random set on first title, second abstract, and finally full text to determine eligibility. The full text articles were critically reviewed and judged by all reviewers. Any disagreement between reviewers was discussed by the full

review team until consensus was achieved. The selected articles were evaluated using a standardized predesigned form listing whether the inclusion criteria were met.

A thorough review process was carried out for the data quality assessment, which consisted of the following three steps.

Step 1: Data abstraction

The Cochrane data abstraction form for intervention reviews (RCTs and non-RCTs) was used as a tool to extract data on study design and methodological quality (appendix 2) [18]. Furthermore, data on the target group, main results, main outcome measures, data source, geographical setting and funding sources was abstracted.

Step 2: Rigor of QI intervention

The included studies were evaluated using the Quality Improvement Minimum Quality Criteria Set (QI-MQCS) as a critical appraisal instrument, developed by the RAND Corporation (appendix 3) [19]. The QI-MQCS contains 16 domains to evaluate the QI intervention, resulting in a scoring system to evaluate whether this domain was met or not. The QI-MQSC did not introduce a threshold concerning acceptability of the quality of the papers. Therefore, we agreed on the following criteria in order to adequately interpret the QI-MQSC score. The study was considered to be of perfect quality (>15 items ranked yes), good quality (>12 items ranked yes), moderate quality (>9 items ranked yes) and insufficient quality (≤ 9 items ranked yes).

Step 3: Rigor of data collection and analysis

In addition to the QI-MQCS, 13 items were added for further evaluation. Two questions (item 2 and 18) from the Downs & Black (1998) criteria were used to reflect on whether the main outcomes to be measured had been clearly described in the introduction or methods section and whether the statistical tests used to assess the main outcomes were appropriate [20]. In addition, three questions (item 10c, 11a and 11b) from the SQUIRE guidelines were used: 1) whether a method was employed for assessing completeness and accuracy of data, 2) whether quantitative methods were used to draw inferences from the data and 3) whether methods were applied for understanding variation within the data, including the effects of time as a variable [21]. Furthermore, it was evaluated how the included studies dealt with missing values, whether they performed audits, reported on secular trends, performed case-mix adjustments, whether clear inclusion and exclusion criteria had been defined for the patient population and when possible whether a power analysis was conducted.

In conclusion, the Cochrane data abstraction form was used to abstract data from the selected articles in order to identify changes in outcomes and facilitators. Data synthesis was guided by 1) the QI-MQCS results, 2) the merged and modified version of the Downs & Black (1998), SQUIRE guidelines, and self-developed questions. Due to the diversity of outcomes, a pooled effect of the results was not conducted.

RESULTS

Search Results and Included Studies

The final systematic search resulted in 11524 records for initial screening; 117 articles were included to review the full text version of which 96 studies were excluded because they did not meet the inclusion criteria (Figure 1) [22]. One additional article was included from a relevant systematic review, which emerged from hand-searching [23,24]. Table 1 presents the characteristics of the 21 included studies. The studies focused on registries for the following patient groups; patients with diabetes [24–31], children with chronic conditions [32], patients with lung cancer [33,34], patients with cystic fibrosis [35–37], patients with cardiac anomalies [38], patients undergoing cardiac surgery [39–41], patients with acute myocardial infarction [42], and patients referred for home health services [43]. The majority of the registries presented voluntary participation [25,26,41–43,27,29–31,35,36,38,40]. Three registries required mandatory participation [28,33,34]. Most of the presented registries had the purpose of achieving QI [24,25,39,41–43,28–34,37]. The remaining studies have introduced their clinical registry for research and educational purposes [26,27,35,36,38,40,44].

Impact of quality improvement

Eight studies showed statistically significant improvement in outcomes resulting from the implementation of QI initiatives [25,27,29,31,33,34,42,44]. Statistically significant improvements were achieved in long-term survival [33,34], mortality [42], readmission rate [42], bleeding complications [42], systolic blood pressure [27], HbA1C [27,29], LDL [27,29], exercise habits [25], depression improved in the acute phase (PHQ-9 score) [44], and hospitalization with ambulatory care-sensitive conditions [31]. The remaining studies did not show statistically significant improvements. All included studies presented outcome measures for their respective improvement work, five of which also measured additional process measures [27,28,45,29–33,35,41,44]. Table 2 presents outcomes measures used, QI methods applied and whether statistically significant improvement of outcome measures was achieved. A detailed overview of the significance of outcome measures can be found in appendix 4. None of the studies identified an impact on patient value or evaluated the impact on costs of care.

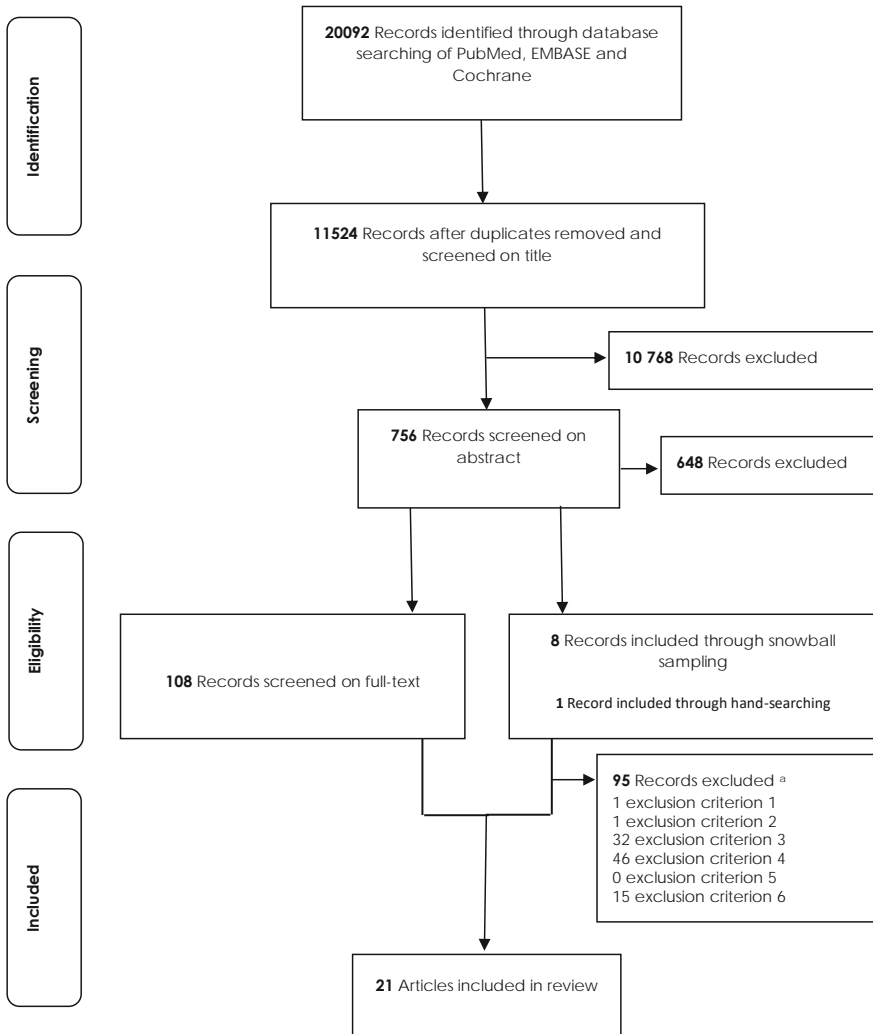


Figure 1. Flow diagram

Source: Authors' analysis, format source from PRISMA [22]

Notes: ^a Exclusion criteria: 1. Studies published in peer-reviewed journals; 2. Studies published in English; 3. Did not actively implement a strategy making use of outcome data to realize quality improvement; 3. Did not rely on structural data collection; 5. Did not evaluate quality improvement interventions using data from outcome registries.

Table 1. Characteristics of Included Studies (n=21).

Characteristics	No. (%)
Geographical setting	
United States [24,25,39–41,43,44,27–29,31,32,35,37,38]	15 (71.0%)
Sweden [26,42]	2 (9.5%)
Denmark [33,34]	2 (9.5%)
Germany [36]	1 (4.8%)
Singapore [30]	1 (4.8%)
Target group	
Diabetes [24–31]	8 (38.1%)
Depression [44]	1 (4.8%)
Children with chronic conditions [32]	1 (4.8%)
Lung Cancer [33,34]	2 (9.5%)
Cystic fibrosis [35–37]	3 (14.3%)
Congenital heart disease [38]	1 (4.8%)
Myocardial infarction [42]	1 (4.8%)
Patients undergoing cardiac or cardiothoracic surgery [39–41]	3 (14.3%)
Patients referred for home health services [43]	1 (4.8%)
Study design	
Observational study [29–31,33–37,39,41]	10 (47.6%)
Randomized-Controlled Trial [24,25,27]	3 (14.3%)
Case study [26,28]	2 (9.5%)
Cohort study [38]	1 (4.8%)
Before and after study [32,40,42]	3 (14.3%)
Quasi-experimental study [44]	1 (4.8%)
Prospective evaluation study [43]	1 (4.8%)
Funding sources	
National funding [25,27,28,31,32,36,42,43]	8 (38.1%)
Private funding [24,29,35,37,44]	5 (23.8%)
Unknown [26,30,33,34,38–41]	8 (38.1%)
Registry participation type	
Voluntary [25,26,41–43,27,29–31,35,36,38,40]	13 (62.0%)
Mandatory [28,33,34]	3 (14.3%)
Unknown [24,32,37,39,44]	5 (23.8%)
Registry purpose	
Quality improvement [24,25,39,41–43,28–34,37]	14 (66.7%)
Research and education [26,27,35,36,38,40,44]	7 (33.3%)
Quality improvement efforts	
Benchmarking [33,34,38–40]	6 (28.6%)
Plan-do-check-act (PDCA) [36]	2 (9.5%)
Collaborative Care Model [26,28,42,44]	4 (19.0%)
The Chronic Care Model [25,32]	2 (9.5%)
Learning and Leadership Collaborative [35]	1 (4.8%)
Plan-do-check-act (PDCA) and the Chronic Care Model [37]	1 (4.8%)
IT application as feedback tool [24,27,30,41]	4 (19.0%)
No clear QI method [29,31,43]	3 (14.3%)

Table 2. Improvement in outcomes and/or processes.

Author/year	Outcome measures	Significant improvement +1/0 ² /0 ^{a3}	RAND QI-MQCS score	QI methods	QI focus
Dziuban et al., (1994) [39]	Risk adjusted mortality	0 ^a	12	Benchmarking	Hospital-specific and physician-specific results published annually in cardiac surgery.
Adams et al., (1998) [43]	Ambulation/locomotion	0	10	No clear QI method	Implementation of and outcome-based quality improvement concept including two outcome reports.
	Bathing	0			
	Management of oral medications	0			
	Pain	0			
	Dyspnea	0			
Halpin et al., (2004) [40]	Postoperative Atrial fibrillation	0 ^a	11	Benchmarking	Implementation of a new guideline based on insights into outcomes, literature and roundtable discussion. An Outcome Center was formed and a multidisciplinary Performance Improvement Committee.
	Operative mortality	0			
	Cardiac arrest	0			
	Reoperation for bleeding	0			
	Pneumonia	0			
	Deep sternal infection	0			
	Permanent stroke	0			
	Transient stroke	0			
	Prolonged ventilation	0			
	Length of stay	0			

Table 2. Continued.

Author/year	Outcome measures	Significant improvement $+1/0^2/0^{a.3}$	RAND QI-MQCS score	QI methods	QI focus
Moller et al., (2005) [38]	Overall operative Mortality	0 ^a	7	Benchmarking	Developed a centralized data acquisition and analysis method (through the creation of the network pediatric Cardiac Care Consortium). A uniform diagnostic and procedure classification system was created. Differences in patient populations cared for at the cardiac centers were compared.
Thomas et al., (2007) [24]	HgbA1c LDL cholesterol Blood pressure	0 0 0	13	IT application as feedback tool	Registry-generated audit, feedback and patient reminder targeted at residents.
Peterson et al., (2008) [27]	Mean systolic blood pressure HbA1c Mean LDL	+ + +	10	IT application as feedback tool	Multicomponent intervention: implementation of an electronic diabetes registry, visit reminders, and patient-specific physician alerts.
Carlhed et al., (2009) [42]	Mortality Readmission rate Bleeding complication	+ + +	12	Collaborative Care Model	Multidisciplinary teams consisted of critical care unit nurses and cardiologists were assigned at each of the 19 volunteering hospitals. 19 teams of 4 to 5 persons met at 4 (group A) or 2 (group B) training sessions during which education by QI experts was provided, using the Breakthrough Series curricula.

Table 2. Continued.

Author/year	Outcome measures	Significant improvement +1/0 ^a /0 ^a 3	RAND QI-MQCS score	QI methods	QI focus
Jakobsen et al., (2009) [33]	1-year survival	+	5	Benchmarking	Indicators (staging, surgical procedures, complications and survival) have been registered in 5007 patients who underwent surgery. Each year the results have been audited locally, regionally and nationally and improvements have been proposed, implemented, monitored and evaluated by the audit-plenary.
	2-year survival	+			
	5-year survival	0			
	30-day mortality	0 ^a			
Kraynack et al., (2009) [35]	FEV1	0 ^a	12	Learning and Leadership Collaborative	A QI process is described from the initial team-building phase, through the assessment of care processes, standardization of care, and developing a culture of continuous improvement aiming to improve pulmonary function of the pediatric patients.
MacLean et al., (2009) [25]	Blood pressure	0	10	The Chronic Care Model	Providing decision support and patient decision support in diabetes care delivery.
	BMI	0			
	SF-12 Physical	0 ^a			
	SF-12 Mental Quality of life	0			
	Exercise habit	+			
	Poor HbA1c (9% and above)	0 ^a	11	IT application as feedback tool	Chronic disease management system with patient reminders based on registry data.
Toh et al., (2009) [30]	Good LDL-control below 2.6 mmol/L	0 ^a			

Table 2. Continued.

Author/year	Outcome measures	Significant improvement +1/0 ² /0 ^{a.3}	RAND QI-MQCS score	QI methods	QI focus
Baty et al., (2010) [29]	% with HbA1c <7% % with HbA1c <9% %with LDL <100	+ + +	10	No clear QI method	Implementing a comprehensive system-based disease management process including a diabetes registry and quality reports.
Beaulieu et al., (2010) [41]	Mortality	0 ^a	7	Benchmarking IT application as feedback tool	Implementing a method for linking administrative and registry data to track quality improvement initiatives through dashboards.
Bricker et al., (2010) [28]	Infusion rate A1C Blood pressure LDL Cholesterol levels	0 ^a 0 ^a 0 ^a	9	Collaborative Care Model	Implementing the Chronic Care Model through regional care learning collaborative with focus on team-based care, patient-centered care coordination, delivery of evidence-based care, patient self-management, use of a patient registry system and culturally and linguistically competent care.
Bauer et al. (2011) [44]	Depression improved in acute phase (PHQ-9 score)	+	12	Collaborative Care Model	Implementing a collaborative care model including a web-based disease registry, care management to support treatment and organized psychiatric consultation.

Table 2. Continued.

Author/year	Outcome measures	Significant improvement +/0 ^a /0 ^a ³	RAND QI-MQCS score	QI methods	QI focus
Stern et al., (2011) [36]	A1C testing	0	10	Plan-do-check-act (PDCA)	Realizing continuous quality improvement through benchmarking in cystic fibrosis care.
	FEV1 > 80 < 18	0 ^a			
	FEV1 > 80 > 18	0 ^a			
	BMI > 19	0 ^a			
	WH > 90	0 ^a			
Jakobsen et al., (2013) [34]	1-year survival	+	5	Benchmarking	Indicators were established, validated, and monitored. 40,000 patients have been included in the database. Results were reported periodically and submitted to realize auditing on an annual basis.
	2-year survival	+			
	5-year survival	+			
Siracusae et al., (2014) [37]	Median FEV1	0 ^a	13	Plan-do-check-act (PDCA) The Chronic Care Model	Several improvement interventions implemented between 2001 and 2007 with focus on patient and family engagement in CF care, improve access and use of data, individualized scheduling, improving vaccination rates, infection control airway clearance, standardization of care processes, and forming and QI team.
	Median body mass index (BMI)	0 ^a			The effect of 23 diabetes teams joining a quality collaborative on patient outcomes.
Peterson et al., (2015) [26]	Systolic blood pressure	0 ^a	13	Plan-do-check-act (PDCA) Collaborative Care Model	
	HbA1c	0 ^a			
	LDL	0 ^a			

Table 2. Continued.

Author/year	Outcome measures	Significant improvement + ¹ /0 ² /0 ^{a3}	RAND QI-MQCS score	QI methods	QI focus
Han et al. (2016) [31]	Hospitalization with ambulatory care-sensitive conditions ED visits	+ +	7	No clear QI method	Using clinical registry data to identify patients who should receive reminders for preventive/follow-up care and send reminders to those patients. Generate a list of patients by condition to use for quality improvement.
Lail et al., (2017) [32]	Disease remission Disease control Quality of life Symptom management	0 ^a 0 ^a 0 ^a 0 ^a	13	The Chronic Care Model	Eighteen condition teams implemented interventions varying from: establishing pre-visit planning (PVP), identifying the target populations, selecting and measuring outcomes and supporting processes, building and implementing care coordination, and assessing and addressing self-management support. The teams were free to choose the interventions that they thought would work best.

¹ + means that the result was statistically significant at a p-value of 0.05.

² 0 means that there was no significant improvement in outcomes.

³ 0^a means that there was improvement, but significance was not tested or reported.

Quality of the studies

Rigor of quality improvement interventions

The overall quality of included articles was moderate (table 3-A and table 3-B). On the 16 domains of the QI-MQCS four articles achieved a score of 13, which is the highest score among included studies [24,26,32,37]. These articles are therefore considered to be of good quality. Four articles were ranked as moderate quality with a score of 12 [35,39,42,44]. Five articles scored poorly on the QI-MQCS with a score ≤ 7 , which is ranked as low quality [31,33,34,38,41].

Rigor of data collection and analysis

The overall results of the quality assessment on data collection and analyses are displayed in appendix 5. Four studies have applied generalized linear mixed models for the analysis of change in outcomes [25,27,36,42]. One study used as generalized estimating equations model with repeated measurements [24]. Inferential statistics have also been used in the form of survival analyses, logistic regression and chi-square analyses [29,31,33,39,44]. The remaining studies made use of descriptive statistical analyses only [26,30,32,38,43]. In order to monitor change run charts have been applied in five studies [28,35,37,40,41].

On the additional item criteria, two studies have applied methods to account for missing values in their data, while also conducting a power analysis [25,27].

Table 3-A. Scoring of the RAND QI-MQCS.

	Dziuban et al., (1994) [39]	Adams et al., (1998) [43]	Halpin et al., (2004) [40]	Moller et al., (2005) [38]	Thomas et al., (2007) [24]	Carlfhed et al., (2008) [42]	Peterson et al., (2008) [27]	Jakobsen et al., (2009) [33]	MacLean et al., (2009) [25]	Kraynack et al., (2009) [35]
1. Organizational motivation	Y	Y	Y	N	Y	Y	N	N	N	N
2. Intervention rationale	Y	Y	Y	Y	Y	Y	Y	N	Y	Y
3. Intervention description	Y	N	Y	Y	Y	Y	Y	N	Y	Y
4. Organizational characteristics	Y	Y	Y	N	N	Y	N	N	Y	Y
5. Implementation	Y	N	Y	Y	Y	Y	Y	N	Y	Y
6. Study design	Y	Y	N	N	Y	Y	Y	Y	Y	Y
7. Comparator	Y	N	Y	N	Y	Y	Y	N	Y	Y
8. Data source	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
9. Timing	Y	Y	Y	N	Y	Y	Y	N	Y	Y
10. Adherence and fidelity	N	N	Y	N	N	N	N	N	N	Y
11. Health outcomes	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
12. Organizational readiness	Y	N	Y	N	Y	N	N	N	N	Y
13. Penetration and reach	N	N	N	N	N	Y	Y	Y	Y	N
14. Sustainability	N	Y	N	Y	Y	N	N	N	N	N
15. Spread	N	Y	N	Y	Y	N	N	N	N	Y
16. Limitations	Y	Y	N	N	Y	Y	Y	Y	N	N
Total score (Y)	12	10	11	7	13	12	10	5	10	12

Table 3-B. Scoring of the RAND QI-MQCS.

	Bricker et al. [28]	Beaujieu et al. [41]	Bauer et al. [44]	Stern et al. [36]	Jakobsen et al. [34]	Siracusa et al. [37]	Peterson et al. [26]	Han et al. [31]	Lail et al. [32]	Toh et al. [30]	Baty et al. [29]
1. Organizational motivation	N	Y	Y	N	N	Y	N	N	Y	Y	Y
2. Intervention rationale	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
3. Intervention description	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
4. Organizational characteristics	N	N	Y	Y	N	Y	Y	N	N	N	Y
5. Implementation	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y
6. Study design	Y	N	Y	N	N	N	Y	N	N	N	N
7. Comparator	Y	N	Y	Y	N	Y	Y	Y	N	Y	Y
8. Data source	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
9. Timing	Y	N	Y	Y	N	Y	Y	Y	Y	Y	N
10. Adherence and fidelity	N	N	N	N	N	Y	Y	N	Y	N	N
11. Health outcomes	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
12. Organizational readiness	N	Y	Y	N	N	Y	N	N	Y	Y	Y
13. Penetration and reach	Y	Y	N	N	Y	Y	N	N	Y	N	N
14. Sustainability	Y	N	N	Y	N	Y	Y	N	Y	N	N
15. Spread	N	N	N	Y	N	N	Y	N	Y	Y	N
16. Limitations	N	N	Y	N	N	N	Y	Y	Y	Y	Y
Total score (Y)	9	7	12	10	5	13	13	7	13	11	10

Notes: Based on the Quality Improvement Minimum Quality Criteria Set (QI-MQCS) developed by the RAND Corporation [19].

Methods used to achieve improvements

We identified six methods to achieve QI: benchmarking [33,34,38–41], a collaborative care model [26,42,44], Plan-Do-Check-Act [36], the Chronic Care Model [25,28,32,37], Learning and Leadership Collaborative [35] and IT driven interventions [24,27,29–31]. There were some studies where no clear QI method was used [29,31,43]. We will discuss these methods in the following paragraphs.

Benchmarking

Benchmarking has been applied in several of the included studies [33,34,38,39,41]. Data was mostly compared among different hospitals [33,34,38]. Annual publication of data in the form of reports has most commonly been applied to report on results [33,34,41].

One study complemented their national report with an additional disease specific report with supplementary measures [33]. Another method of benchmarking used was a discussion of the results at a (monthly or annual) meeting [28,38,40,41]. During the annual meeting, results from reports were discussed and further evaluated [38]. Also, short-term feedback cycles with monthly publication of reports were applied [39]. The use of a strong data-driven system in combination with audits was characteristic of initiatives that applied benchmarking in order to improve outcomes as well as a model to change practice [33,34,39,40].

Collaborative Care Model

Three studies applied the Breakthrough Collaborative Model (BCM) to structure the goal of improving outcomes [26,28,42]. One study applied a Web-based disease registry to track patients with symptoms of depression to support treatment management in primary care [44]. In addition, evidence-based depression management training was provided to primary care providers. Moreover, in all sites, most patients experienced meaningful improvement in depression.

The BCM was used to design a cycle of structured discussion sessions during which outcomes were analyzed, presented and variation in work processes were discussed [26,28]. The model was furthermore used as a guide to facilitate improvement efforts and insights into data [26,42].

Plan-Do-Check-Act

In two studies Plan-Do-Check-Act (PDCA) cycles were used to improve outcomes and/or processes [26,36,37]. Yet, the cycle was presented as a supporting tool to other methods, either for the application of the BCM [26] or for benchmarking [36]. For the latter it was applied as a method to prepare for national benchmarking by organizing

three PDCA cycles before data was shared [36]. The method was applied by organizing multidisciplinary meetings, where outcomes were discussed and improvement initiatives were identified [36]. Three cycles were organized in order to prepare public benchmarking after the third cycle [36].

The other study, which primarily used the methods outlined for the BCM, used the PDCA to structure and evaluate the learning sessions [26]. However, it was not the primary method for improving outcomes. In another study PDCA was used to continually evaluate local cystic fibrosis care practices, and they were able to improve pulmonary function and nutritional outcomes [37].

The Chronic Care Model

Three studies applied the Chronic Care Model (CCM) [25,28,32,37]. One study that applied the CCM used supporting techniques such as: audit and feedback, electronic registry, clinician reminders, patient reminders, and abbreviated patient education. It is, thus, rather a framework offering practical tools [25]. They did not find expected improvements in outcomes. Here, authors suggested that another, more collaborative approach would be needed to improve outcomes of chronic diseases [25]. The second study applied the CCM in children with various chronic conditions, in combination with PDCA cycles, failure mode and effect analysis and Pareto charts of failures [32]. This study resulted in improvement of respective outcomes [32]. The third study applied the CCM to ensure that all aspects of cystic fibrosis management were covered, and combined this with the PDCA to continually evaluate the processes of best practices in cystic fibrosis care. They did not evaluate the effectiveness of applying the CCM.

Learning and Leadership Collaborative

The Learning and Leadership Collaborative (LLC) was applied in one study [35]. Commitment of a team to participate in a QI program, developing a sense of common responsibility as an organization for the improvement, measuring outcomes and processes and patient involvement were defined as key ingredients for QI. LLC has been used for training staff towards structured discussions on outcomes and/or processes and the introduction of a patient registry [35]. Data was registered and analyzed at one particular hospital, but presented to all participating hospitals. Participation in the LLC has led to the initiation of an improvement initiative at the hospital where the data were registered and analyzed.

IT application as feedback tool

Five studies made use of (self-developed) IT applications, to empower patients and/or physicians to manage patients with greater care. The studies aimed at linking

administrative and key clinical data and made use of reminder functions [24,27,30]. One study concluded their patients received better overall coordination of care [30]. Another two studies reported significant improvements in the percentage of type 2 diabetic patients and at-risk populations utilizing diabetes registries achieving recommended values for SBP, LDL, and HbA1C [27]. In one study, data were in addition displayed in operating room theatre, surgical office suites and nursing units [41]. Another study reported improved adherence to diabetes care processes in a continuity clinic due to the registry-generated audit, feedback, and patient reminders [24].

Facilitators for quality improvements

A noticeable facilitator leading to QI was frequent reporting and feedback either annually or even monthly [28,33,34,38–41]. The use of a database with high quality data, audits and reports as well as a strong stakeholder involvement were also found to be important factors contributing to successful QI [33,34]. Structured registry data and an improvement intervention that can be linked to outcomes led to improvement in respective outcome measures [42]. In addition, other factors mentioned that would be needed for successful QI in one or more of the included studies are (1) patient involvement, communication, and standardization; (2) attitude and enthusiastic commitment from physician leadership, clinical managers and central administration and (3) appreciation concerning the importance of measurements [28,35,40,41]. Moreover, improvement in outcomes appeared to be successful if supported by a proven QI approach [42]. Inconsistencies were found regarding the importance of involving an expert in the field of QI. On the one hand, involvement of a QI expert was considered positive for the start of an improvement agenda as it contributed to a more rapid implementation of improvement initiatives [42]. On the other hand, involving no additional expert or formal team was not experienced as a contributing factor to the success of outcome improvement [26]. This was only possible because a structured data registry was already present [26].

Catalyst to improve outcomes over time

Outcomes can be improved over time through systematic use of outcome registries and facilitators. Outcome data and its interpretation helps to achieve improvements in outcomes over time even faster compared to studies that did not use outcome data [34]. It was stated that outcomes were not only used to identify possible improvement interventions but also to monitor and secure improvements in the long run [34].

A computerized system was presented as a success factor to accelerate data from clinical registries to change outcomes and/or processes [24,26,36,42,27–29,31–35]. Such a computerized system ensured valid and timely results [33]. Moreover, it allows for real-time feedback, which, in turn, leads to faster identification of improvement areas [28,29,31,42].

Further use of outcome data for outcome improvement included the development of checklists, improved use of diagnostic standards, creation of data transparency, guidelines, improved patient recall and empowerment and discussions and leadership towards improvement [28,29,31,36].

DISCUSSION

Eight out of the 21 included studies reported statistically significant improvements in outcomes including long-term survival, mortality, readmission rate, bleeding complications, systolic blood pressure, HbA1C, LDL, exercise habits (FEV1), depression improved in the acute phase (PHQ-9 score) and hospitalization with ambulatory care-sensitive conditions resulting from the implementation of QI initiatives. Out of these eight studies, the Chronic Care Model, IT application as feedback, benchmarking and the Collaborative Care Model were used as QI methods. A diverse set of clinical outcomes were collected and no patient-reported outcome measures (PROMs) were applied in any of the studies. Yet, only one study that reported statistically significant improvements in outcomes was of good quality. The improvement interventions were diverse, ranging from the implementation of guidelines, development of physician/patient alerts, improved teamwork, patient engagement methods through IT applications and the development of a supportive decision system. Many improvement interventions were combined in order to build a multifaceted approach to QI [24,27,28,32,37,42,44]. Facilitators for realizing QI include a high quality database, the use of pre-defined outcome measures, audits, frequent reporting and feedback, patient involvement, improved communication and standardization. Systematic approaches were used for structuring the improvement cycle. In order to use data from clinical registries as a catalyst to change outcomes, this review suggests that having a strong computerized system is supportive in aiding frontline clinical process management and improvement work.

A facilitator identified in this review was the organization of discussions for mapping and selecting best practices. It was further shown that a sound data management has a catalyzing effect. This data can be aggregated in annual reports, while it can also be used to compare with peers and/or perform nationwide comparisons. Also, a registry can facilitate access to real-time outcome and process data which can engage the team in realizing active improvements. Other registry programs such as the Get With The Guidelines-Stroke study, a large registry and performance improvement program for hospitalized patients with stroke and transient ischemic attack, also use annual reports for benchmark and feedback purposes [46].

Other systematic reviews concluded that audit and feedback can lead to small but important improvements in professional practice and healthcare outcomes [47]. They furthermore concluded that the effectiveness of audit and feedback depends on how the feedback was provided as well as on baseline performance. In addition, comparing this review to ours, there was one paper we have both included [24]. However, the objectives are very different, which can explain there was not more overlap in included studies.

In addition, barriers and success factors to the effectiveness of feedback have been identified [48]. However, the authors were not able to draw sound conclusions on the effect of feedback on the quality of care and its potential to improve outcomes. Another review concerning renal registry data reflected on the potential of registry data and help advancing the nephrology care delivery [49].

None of the reviews studied the effect of QI efforts, besides from audit and feedback, on the quality of care and outcomes. This is the first study for which the literature was searched in detail in order to identify barriers and facilitators supporting QI interventions based on information from clinical registries.

The use of clinical registries can be seen as an important tool in order to systematically measure clinical outcomes and to achieve the goals of value-based health care. This is not only in line with our conclusions, but also acknowledged by others [1,50,51]. Other data sources can also be valuable for QI efforts, such as data from randomized controlled trials. However, this review aimed at including studies where structural data was collected through the use of a clinical registry.

In order to improve value, measuring both one or more outcomes and costs is essential [50]. Working with international registries makes it possible to make global comparisons, for example identifying practice variations and therefore improving quality of care for the whole patient group [52].

Implications

We did not observe many efforts to incorporate patient reported outcome measure (PROMs). It is, however, generally considered important to measure the impact on health related quality of life (HRQoL) in the evaluation of the effect of QI initiatives [53]. The studies included for this review did not reflect on why they did not use PROMs and what would be the added value if they did. Even so, one study does report however the start of measuring quality of life in patients with cystic fibrosis [36]. The authors report this will lead to more insights into the complexity of QI efforts and personal patient gains in the experienced quality of life. It will also enable reporting on to what extent value was created from

the patient's perspective. Future QI efforts very likely combine QI with benchmarking incorporating quality of life outcomes.

None of the included studies reported costs, causing our study to be unable to evaluate the true impact on value. Incorporating costs will enable to identify cost drivers and comparing improvement interventions as proposed by the value-based healthcare principles [50]. A recent study showed that surgery for the oldest patients with colorectal cancer did not lead to increased hospital costs [51]. However, this study did identify variation in cost driver distribution. Patients under 85 years old had lower costs looking at the ward, operation and intensive care unit. Therefore, identifying costs and its main drivers will enable to develop improvement programs for specific sub-groups. This might be a powerful tool to reduce e.g. complications and thus hospital costs. Value-based health care could be the overarching concept guiding improvement initiatives, combined with the well-defined methods. However, the field lacks a clear guide on implementation examples. Studies reflecting on impact, outcomes and costs are needed. Finally, the standardization of outcome measures is key, although they should be defined for a specific patient population. Transparent measurement of outcomes and costs has the potential to improving the value of care for all patients. Both providers, patients and payers can benefit from this collective common goal of transparency.

Limitations

This review has some inherent limitations. Firstly, due to the very heterogeneous types of QI programs and their respective patient groups, it is difficult to generalize the results achieved in the included studies. Moreover, our inclusion criteria for QI programs may be to some extent arbitrary, which could possibly lead to a bias in inclusion or exclusion of studies.

Also, the context in which the clinical registry is organized can impact outcomes. Moreover, important differences were observed in e.g. whether the registry was linked to reimbursement or public reporting versus primarily initiated for scientific or QI purposes or whether it was a voluntary or mandatory registry.

Secondly, the studies included in this review mainly focused on experiences in non-communicable diseases and thus often chronic patient groups. However, our aim was not to exclude communicable diseases from the study but we did not identify any studies in our literature search. This could indicate that chronic patient groups benefitted most from the realization of registries and respective QI interventions. As a result, improvement projects concerning other (non-chronic) patient groups have not been included in this review. Thirdly, due to publication bias, studies reporting no effect will be very likely not

published and therefore missed out. Finally, two studies randomized practices [25,27]. One study randomly allocated 19 volunteering hospitals to 1 of 2 intervention groups, where the intervention differed both in design and intensity [42]. In the other studies it should be noted that complete randomization was not possible, since the intervention hospitals involved were e.g. volunteering. Therefore, these hospitals might differ in their willingness to improve, causing potential selection bias.

CONCLUSIONS

The results from this evaluation of studies which use outcome measures from clinical registry data to implement and monitor QI initiatives may help policy makers, managers and clinicians to understand the effectiveness, practicality and challenges of implementing QI interventions. An active and systematic approach is needed to improve outcomes. Continuous feedback from the data linked to clinical practice is crucial. Our review indicates that successful QI and consequently improved outcomes, is dependent on an active approach and organizational readiness.

There are many QI methods, and the majority of improvement interventions contain a combination of several methods. Clinical registries can be seen as supportive instruments in the process of improving quality of care. However, a clinical registry can only be successful in realizing QI efforts when there is commitment and leadership at both the physician and manager level, as well as a benchmarking facility, a well-integrated computerized system, and a collective aim to identify best practices.

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SUPPLEMENTAL SECTION

Supplemental Table S1. Search string PubMed, Embase and Cochrane (p. 2-3).

Supplemental Table S2. Data collection form for intervention reviews: RCTs and non-RCTs (p. 4-19).

Supplemental Table S3. Quality Improvement Minimum Quality Criteria Set (QI-MQCS) items (p. 20-21).

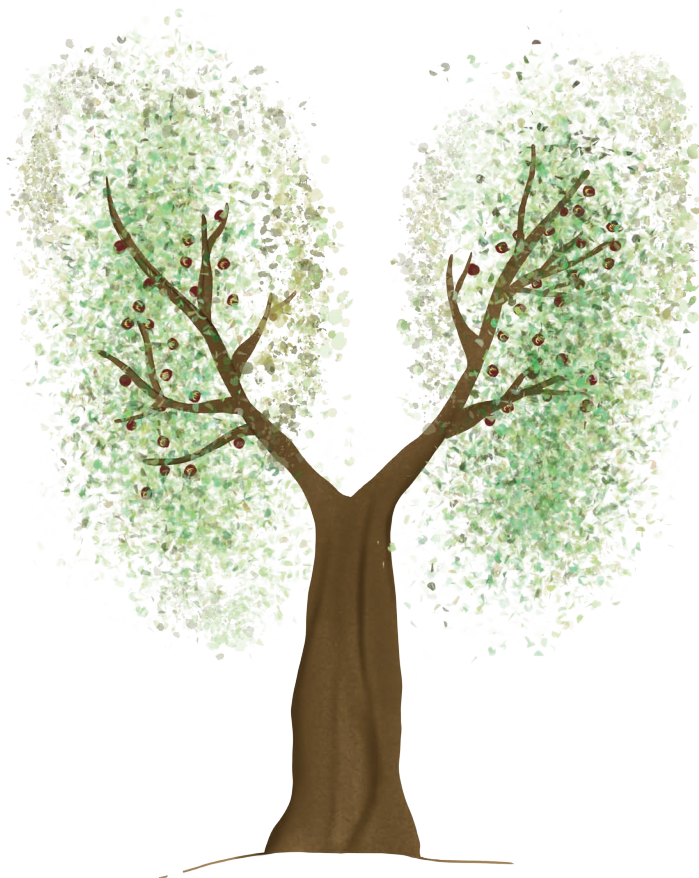
Supplemental Table S4. Detailed summary of included studies (p. 22-26).

Supplemental Table S5a. Scoring of the Downs & Black criteria, SQUIRE guidelines and additional self-developed tool (1/2, p. 27-29).

Supplemental Table S5b. Scoring of the Downs & Black criteria, SQUIRE guidelines and additional self-developed tool (2/2, p. 30-32).

This supplementary material provides additional information about the presented review. The listed supplemental sections can be downloaded from the additional files section online:

<https://bmchealthservres.biomedcentral.com/articles/10.1186/s12913-018-3828-9#Sec24>



Development and
Evaluation of the Outcome
Indicator Set for Pulmonary
Sarcoidosis

Part





A First Patient-Centered Set of Outcomes for Pulmonary Sarcoidosis: a Multicenter Initiative

3

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ABSTRACT

Background: 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. The opinion of healthcare professionals was measured using a mixed-method approach for the identification of an outcome measures set and initial conditions for patients with pulmonary sarcoidosis. During a ranking process, participants were instructed to rank variables on a scale from 1-10 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 (sIL-2R) 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 etiology, characterized 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).[1] A chronic disease course requires long-term treatment with corticosteroids, cytotoxins and other agents that can have a serious impact on the quality of life.[2] Significant grey areas exist in approaches to treatment and thus how care is delivered across different countries and centers.[3] Little knowledge is available regarding outcomes of delivered care in relation to the various treatment options. Therefore, there is a need for standardization 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.[4] 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.[5] 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.[6]

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.[7, 8] 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.[2, 9-11] Spontaneous remissions occur in approximately two-thirds of the patients, but the disease course is chronic in 10%–30% of the patients.[9] 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.[9, 12] For this study, we aimed to specifically develop a standard set of outcome measures for patients with pulmonary sarcoidosis.

In order to optimize treatment to the individual patient with sarcoidosis, the availability of center-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 centers.[13] Globally, there is a broader interest in studying the within-hospital as well as the between-hospital variation in various medical conditions. [14, 15] 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-centered 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 recognized 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 (Appendix 1).[16, 17] 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,[2, 18] 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 [9]: (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 (i.e., sustainability of health or recovery and long-term consequences of therapy).[8]

The development of the set was structured in three main phases. First, as introduced by Kaplan & Porter,[8, 19] 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). [20, 21] 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 prioritized. A structured consensus-driven, RAND-modified Delphi method was employed to prioritize 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 prioritizing 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 prioritization emerged, they were openly discussed until consensus was reached.

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 (appendix 4). Next, outcome

measures were ranked based on the *Meetbaar Beter* criteria delineated earlier.[20, 21] 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 prioritized 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.

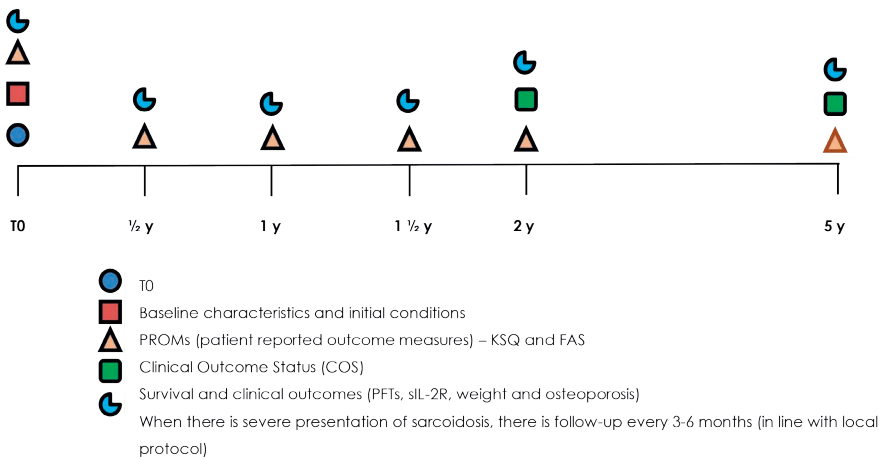


Figure 1. Suggested timeline for collecting outcomes

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.

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. FEV1% 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 measurement 2. sIL2R (measured in pg/ml, limit >3000)	Every visit to the clinic	Clinical
4. Weight gain	Clinical monitoring	Weight in kg measured at each PFT	Every visit to the clinic	Clinical
5. Quality of Life; physical functioning	Patient-reported health status	King's Sarcoidosis Questionnaire (KSQ) [22] and the (FAS) [23, 24]	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 [25]</i>	Monitor throughout treating the patient	Clinical
7. Clinical Outcome Status (COS) [26]	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

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 apnea	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	Multi organ involvement [27]	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 [28]	Scadding stage based on chest x-ray	1. Stage 0: normal 2. Stage I: lymph nodes in hilli 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	Socio-economic status	Postal code	Administrative

Tier 1: outcome measure 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.[29]. Most deaths are due to pulmonary fibrosis, pulmonary hypertension, neurologic and cardiac involvement.[9].

Outcome measure 2 is pulmonary function (FVC, FEV1 and DLCO_c), which is widely used to monitor disease progression. Currently, serial FVC is considered as the best endpoint to monitor during the course of care for pulmonary sarcoidosis.[30]

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.[31] A shortcoming of 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.[32] However, it outperforms conventional biomarkers such as angiotensin converting enzyme (ACE) [33] and is cheaper and more widely available than sensitive tests like fluorodeoxyglucose PET.[34]

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.[35] 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.[2, 36-38] Globally, corticosteroids, such as prednisone, remain the mainstay of therapy in sarcoidosis.[9, 39] 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/d [40]. However, it remains debated whether prednisone therapy modifies long-term progression of the disease.[41] We chose weight gain as a measure of disutility of care, *outcome measure 4* in the outcome measures set.

Tier 3: outcome measure 5, 6 and 7: sustainability of health (i.e., 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*. The process aims to select well-validated instruments to address the multidimensional outcome domains, minimizing the burden for the patients (e.g., number of questionnaires/questions to fill out) on the one hand, while maximizing 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 (appendix 5 and appendix 6). The FAS is a well-defined and validated questionnaire in patients with sarcoidosis.[23, 24] The cut-off score for presence of fatigue is >21 points.[23] The minimal clinical important difference is defined at a 10% reduction or a change of four points.[44] 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.[45] It consists of 29 questions. The KSQ is available in multiple languages.[22, 45]

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).[26] The COS is defined as *outcome measure* 7 of the set. The aim of applying the COS is to standardize 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).[28] 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 apnea (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.[46] 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 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 apnea) 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 centers. 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. [47] Even low doses of prednisone have been associated with significant morbidity.[37, 38] 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 (FEV1, FVC, DLCOc), sIL-2R change as an activity biomarker, weight gain, quality of life, osteoporosis and clinical outcome status. Routine data collection based on standardized 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-centered 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 multicenter registry, centers 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 centers 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.[48] For example, the GRADS initiative aims to compare blood genomics with clinical phenotypic variables and assess each participant's clinical course during follow-up.[49] 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.[8] 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.[50] Additionally, improved documentation, open communication, encouraging quality improvement and increasing informed decision-making for patients are of great importance when reporting and comparing outcomes.[51] 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.[52, 53]

The set was developed by physicians, as there was a strong need for standardization 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.[21] 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 (e.g., 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 center 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.[54] 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 centers, 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 centers treating patients with pulmonary sarcoidosis.

CONCLUSIONS

The international process resulted in a consensus-driven recommended first set of patient-centered 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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Results of the Standard Set for Pulmonary Sarcoidosis: Feasibility and Multicenter Outcomes

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ABSTRACT

Background: Our study presents findings on a previously developed standard set of clinical outcome data for pulmonary sarcoidosis patients. We aimed to assess whether changes in outcome varied between the different centers and to evaluate the feasibility of collecting the standard set retrospectively.

Methods: This retrospective observational comparative benchmark study included six interstitial lung disease expert centers based in the Netherlands, Belgium, the UK and the USA. The standard set of outcome measures included 1) mortality, 2) changes in pulmonary function (forced vital capacity (FVC), forced expiratory volume in 1 s, diffusing capacity of the lung for carbon monoxide), 3) soluble interleukin-2 receptor (sIL-2R) change, 4) weight changes, 5) quality-of-life (QoL) measures, 6) osteoporosis and 7) clinical outcome status (COS). Data collection was considered feasible if the data were collected in $\geq 80\%$ of all patients.

Results: 509 patients were included in the retrospective cohort. In total six patients died, with a mean survival of 38 ± 23.4 months after the diagnosis. Centers varied in mean baseline FVC, ranging from 110 (95% CI 92–124)% predicted to 99 (95% CI 97–123)% pred. Mean baseline body mass index (BMI) of patients in the different centers varied between 27 (95% CI 23.6–29.4) $\text{kg} \cdot \text{m}^{-2}$ and 31.8 (95% CI 28.1–35.6) $\text{kg} \cdot \text{m}^{-2}$. 310 (60.9%) patients were still on systemic therapy 2 years after the diagnosis. It was feasible to measure mortality, changes in pulmonary function, weight changes and COS. It is not (yet) feasible to retrospectively collect sIL-2R, osteoporosis and QoL data internationally.

Conclusions: This study shows that data collection for the standard set of outcome measures for pulmonary sarcoidosis was feasible for four out of seven outcome measures. Trends in pulmonary function and BMI were similar for different hospitals when comparing different practices.

INTRODUCTION

Reporting outcomes improves healthcare transparency and is increasingly important in daily clinical practice.[1-3] Reporting of outcomes enables quality improvement, optimizes patient safety and improves care and cost-effectiveness. It is important to select outcomes consistently and apply transparent methodologies to ensure data comparison between institutions.[1,4] The patient primarily benefits from increasing the value of care per dollar spent as the key stakeholder.[2,3] In addition, insurers and the healthcare systems as a whole benefit from this.

Globally, the concept of value-based healthcare (VBHC) is embraced by hospitals. VBHC aims to achieve the best possible health outcomes for the lowest cost.[2,3] This concept changes the focus from "volume" to "value" and results in tracking and comparing outcomes.[5,6] The VBHC approach identifies practice variations and best practices in the field, which can be seen as a starting point for further quality improvement.

In sarcoidosis there is a need to define appropriate outcomes for randomized clinical trials (RCTs) and for daily clinical practice to improve the quality of care.[7] We developed a standard clinical outcome set (hereinafter referred to as the standard set) that provides insight in quality of care.[8] However, it is not known whether this set is implementable and unambiguously measurable in centers from different countries. To investigate whether this set can be used to identify clinical differences between interstitial lung disease (ILD) centers, we present retrospectively collected clinical data from six ILD expert clinics in the Netherlands, Belgium, the UK and the USA. This study was designed to assess outcomes of centers with differing patient populations and approaches to management.

The primary objective of this study was to present the standard set of clinical data across the six centers. The secondary objective was to evaluate the feasibility of retrospective data collection of the standard set in practice. Finally, the study aimed to assess whether changes in outcome at 2 years varied between the different centers.

METHODS

Study structure and design

This study is a multicenter retrospective observational cohort study. Six ILD expert centers participated: two from the Netherlands (St Antonius Hospital and Erasmus University Medical Center), one in Belgium (Leuven University Hospital), the UK (Royal Brompton Hospital) and two in the USA (Cleveland Clinic and Cincinnati Medical Center). The feasibility of collecting our predefined standard set was tested using data from these six centers.

For practical reasons, data were collected for a maximum of 100 consecutive patients per center. In order to compare outcome trends between centers, center-specific effects were examined for spirometry variables (forced vital capacity (FVC) % predicted, forced expiratory volume in 1 s (FEV1) % pred), diffusing capacity of the lung for carbon monoxide (DLCO) % pred and body mass index (BMI). Some centers collected less data and were unable to include 100 patients. This was due to the fact the total number of patients that fit the criteria seen within the defined time frame was not always met.

In each center, one or two pulmonologists were involved in the study. They participated in webinars and joined meetings during international conferences to discuss data collection, resulting data and data analyses. These multiple meetings guided the discussion around the implications of the data.

Patient Population

The standard set was designed for patients with pulmonary sarcoidosis, with or without extrapulmonary disease.[9,10] Patients with extra pulmonary involvement only were excluded.

Study population: inclusion and exclusion criteria

We selected patients in line with the following criteria. Patients diagnosed between January 2010 and August 2014; follow-up time after diagnosis was ≥ 2 years; when clinical, radiological and/or bronchoalveolar lavage findings were compatible with the diagnosis, a tissue biopsy was optional; and the definition of pulmonary sarcoidosis patients was in line with the internationally accepted statement on sarcoidosis [11]: 1) the patient has to be diagnosed with pulmonary sarcoidosis, 2) the diagnosis is performed by a pulmonologist.

Patients were excluded when >2 years elapsed between initial diagnosis and first clinic visit and when <2 years of pulmonary function follow-up and treatment had been provided outside of the participating center(s).

Outcome measures

Outcome measures were organized per domain, also referred to as a tier by PORTER and co-workers.[2,3] The three-tiered hierarchy covers different domains of care received by patients during treatment. Tier 1 indicates the health status (survival and degree of health); tier 2 represents the recovery process (time to recovery, disutility of care); and tier 3 covers the sustainability of health (i.e. sustainability of health or recovery and long-term consequences of therapy). Our predefined standard set for pulmonary sarcoidosis includes seven outcome measures. Under tier 1, 1) mortality, 2) changes in pulmonary function (FVC, FEV1, DLCO) and 3) soluble interleukin-2 receptor (sIL-2R) change as an activity biomarker. Under tier 2 we defined one outcome measure: 4) weight changes. Finally, under tier 3, we defined three outcome measures: 5) quality of life (QoL), 6) osteoporosis and 7) clinical outcome status (COS). For osteoporosis, different protocols exist per center. We were unable to evaluate the total number of patients assessed for the risk of developing osteoporosis. We were only able to identify the number of patients who had a dual energy X-ray absorptiometry (DEXA) scan during the respective follow-up period. The COS summarizes different clinical phenotypes of the disease into nine categories.[8] The full background on how this set was developed is described elsewhere.[8]

Pulmonary function tests were performed using Master Screen Body (Jaeger MS-PFT Analyser Unit, Würzburg, Germany), except for Cincinnati Medical Center, where the nSpire machine (nSpire KoKo Legend, model 315002, Longmont, CO, USA) was used. Changes in percentage predicted FVC, FEV1 and DLCO were measured. European Respiratory Society prediction equations for pulmonary function were used by all centers.[12] Changes in pulmonary function over time were then compared according to ethnicity, sex, treatment and center effect.

Feasibility

Feasibility is defined as the "extent to which the required data are readily available or could be captured without undue burden and can be implemented for performance measurement".[13] More specifically, the definition of feasibility in this study was evaluated by estimating, for each outcome measure, the percentage of patients for whom the outcome measure was assessed, out of the total number of patients. An outcome measure was considered feasible if collected on average in $\geq 80\%$ of the patients across centers.

Data Collection

All consecutive patients diagnosed between January 2010 and August 2014 were eligible for this study. Data collection took place between May 2015 and May 2017, resulting in a maximum follow-up time of 96 months. By definition, patients who died within the 2-year follow-up after the diagnosis period were excluded. Data for a maximum of 100 patients

were collected per center. A REDCap database (version 8.1.11; www.project-redcap.org) was constructed by the study coordinator. Every center assigned a data manager to enter outcome measures into REDCap. All required data were extracted manually from the electronic patient records.

Statistical Analysis

All categorical data are presented in n (%) of the total patient group from the respective center. Data on continuous variables are presented as mean±SD. A linear mixed model with a random intercept, random slope was used to estimate trajectories over time for the BMI, and for percentage predicted FEV1, FVC and DLCO. The linear mixed model comprised center, time and the interaction between center and time. The likelihood ratio test was used to evaluate whether insertion of a variable improved the fit of the model. All analyses were performed in SPSS (version 24; IBM, Armonk, NY, USA).

RESULTS

Data from 509 patients were analyzed in this multicenter cohort, including patients from the St Antonius Hospital (n=100), Cincinnati Medical Center (n=55), Cleveland Clinic (n=97), Erasmus Medical Center (n=70), Leuven University Hospital (n=90) and Royal Brompton Hospital (n=97). Feasibility of data collection is shown in table 1. For each center, baseline characteristics are presented in table 2. Mean age at diagnosis varied between 44.3±11.1 years (St Antonius hospital) and 52.1±12.3 years (Cincinnati Medical Center). At the Royal Brompton Hospital, a significantly higher proportion of patients had a Scadding stage IV chest radiograph (n=30, 30.9%), as reflected in low start of the intercept line in the linear mixed model, reflecting worse pulmonary function (figure 1a–c). The outcomes of the standard set are presented in table 3, except for lung function outcomes (figure 1a–c) and BMI trends (figure 2).

Tier 1: outcome measures 1, 2 and 3: degree of health

Mortality

As defined in the criteria, patients who died within the 2-year follow-up after diagnosis were excluded, so no 2-year mortality can be indicated. In our overall follow-up, six patients died from three different centers; in table 3 the mean number of months between the diagnosis and when the patient died are reported. Feasibility analysis showed that this variable was collected for 100% of the patients (table 1).

Pulmonary function

The results of the linear mixed model analyses for pulmonary function are presented in figure 1a–c. There is a yearly average increase of 0.8% for FVC (95% CI 0.4–1.1%), 0.7% for FEV1 (95% CI 0.4–1.1%) and 0.3% for DLCO (95% CI –0.1–0.7%). The patients from the center with the highest FVC started at 111 (95% CI 97–125)% pred and the patients from the center with the lowest started at 99 (95% CI 92–108)% pred. Baseline FEV1 ranged from 98% (95% CI 84–112%) to 86% (95% CI 78–96%). No interaction effect between center and time was observed for average change in FVC, FEV1 and DLCO over a period of 2 years. Although initial pulmonary function differed between centers, the changes in pulmonary function over time did not. Thus, none of the centers differed in pulmonary function test (PFT) trends over time compared to the other centers.

Table 4 indicates that for 69.2–70.1% of the patients, the change from baseline was within –10% and +10% change. There was no difference between centers in the proportion of patients with >10% change in PFT parameters. In addition, the older the patients, the more likely a deterioration of DLCO would be observed ($p=0.004$). Feasibility analysis showed that this variable was collected for 100% of the patients (table 1).

Soluble interleukin-2 receptor

sIL-2R is only routinely measured during follow-up in the St Antonius Hospital. The sIL-2R levels (in $\text{pg}\cdot\text{mL}^{-1}$) were measured in serum with enzyme immunoassays. Table 3 shows mean baseline sIL-2R levels of 87 patients at the St Antonius Hospital (5619 ± 4099 $\text{pg}\cdot\text{mL}^{-1}$). Baseline sIL-2R levels were significantly higher (8241 ± 6344 $\text{pg}\cdot\text{mL}^{-1}$, $p<0.05$) in patients ending up in COS 7–9 ($n=53$) 2 years after diagnosis compared to patients ending up in COS 1–6 ($n=33$, 6232 ± 2438 $\text{pg}\cdot\text{mL}^{-1}$). For the St Antonius Hospital alone, it was a feasible outcome measure as it was collected for 84% of patients; however, data collection for this variable overall was not feasible (measured in 16.5% of the patients) (table 1).

Table 1. Summary of the standard set for patients with pulmonary sarcoidosis.

Standard Set	Feasible* (yes/no)	Measured in patients (n)	Number of Hospitals
Tier 1			
1. Mortality	Yes (100%)	509/509	6/6
2. Pulmonary function	Yes (100%)	509/509	6/6
3. Soluble interleukin-2 receptor (sIL-2R) change as an activity biomarker	No (16.5%)	84/509	1/6**
Tier 2			
4. Weight gain	Yes (81%)	412/509	5/6
Tier 3			
5. Quality of life; physical functioning	No (0%)	0/0	0/6
6. Osteoporosis	nm	nm	6/6***
7. Clinical Outcome Status (COS)	Yes (81%)	412/509	5/6

* The outcome measure was considered feasible when this was measured in >80% of all patients.

** sIL-2R was feasible in the St. Antonius hospital (it was measured in 84% of the patients), in the other centers it was not routinely measured.

*** All centers make use of a local protocol to prevent osteopenia/osteoporosis in high risk patients (in patients with long-term and /or high-dose prednisone use).

nm= not measurable.

Tier 2: outcome measure 4: disutility of care

Weight changes

Results of the linear mixed model analyses for weight changes are presented in figure 2. There is an overall increase of 0.1 (95% CI 0.03–0.21) kg·m⁻² in BMI per year for this specific outcome, which includes data from five out of the six centers. There was no center–time interaction, i.e. no significant differences were seen between centers in BMI changes over time. However, baseline BMI values differed between centers: baseline BMI from Cincinnati Medical Center was 31.8 (95% CI 28.1–35.6) kg·m⁻², while it was 26.8 (95% CI 23.6–29.4) kg·m⁻² in the St Antonius Hospital cohort. It was feasible to collect data on weight changes, as it was collected for 81% of the patients (table 1).

Tier 3: outcome measure 5, 6 and 7: long-term consequences of therapy

Health-related quality of life (QoL)

For this outcome, no structured multicenter data were collected. Health-related QoL was measured regularly in a minority of patients if they were participating in a clinical trial. In addition, some centers only measured QoL once at baseline, when the patient visited the clinic for the first time. In this retrospective study, it was not feasible to collect this outcome measure routinely (table 1).

Table 2. Baseline characteristics of the multicenter study cohort (n=509).

	St. Antonius (n=100)	Cincinnati MC (n=55)	Cleveland Clinic (n=97)	Erasmus MC (n=70)	Leuven UZ (n=90)	Royal Brompton (n=97)
Age at diagnosis (±SD)	44.3 ±11.1	52.1 ±12.3	47.6 ±10.5	44.7 ±11.4	45.4 ±11.4	48.3 ±12.5
Gender (n, %)						
Male	56 (56.0%)	16 (29.1%)	41 (42.3%)	43 (61.4%)	52 (57.8%)	50 (51.5%)
Ethnicity (n, %) §						
White	79 (79%)	44 (80%)	70 (72.1%)	54 (77.1%)	82 (91.1%)	71 (73.2%)
Black	7 (7%)	11 (20%)	25 (25.8%)	11 (15.7%)	1 (1.1%)	0
Other	14 (14%)	0	0	4 (5.7%)	5 (5.6%)	26 (26.8%)
Unknown	0	0	2 (2.1%)	1 (1.5%)	2 (2.2%)	0
Weight at diagnosis (in kg, ±SD)	83.0 ±17.0	88.5 ±24.0	86.9 ±20.7	83.4 ±18.4	86.0 ±22.4	82 ±21.9
BMI at diagnosis (±SD)	26.8 ±4.8	31.8 ±8.1	31.2 ±8.9	27.6 ±5.6	28.0 ±5.3	29.0 ±7.7
Smoking (n, %)						
Never	51 (51.0%)	32 (58.2%)	57 (58.8%)	35 (50.0%)	60 (66.7%)	61 (62.9%)
Ever	33 (33.0%)	18 (32.7%)	36 (37.1%)	24 (34.3%)	22 (24.4%)	30 (30.9%)
Active	11 (11.0%)	3 (5.5%)	4 (4.1%)	11 (15.7%)	8 (8.9%)	6 (6.2%)
Unknown	5 (5.0%)	2 (3.6%)	0	0	0	0
Scadding stage (n, %)						
Stage 0	4 (4.0%)	1 (1.8%)	6 (6.2%)	9 (12.9%)	18 (20%)	6 (6.2%)
Stage I	36 (36.0%)	24 (43.6%)	23 (23.7%)	20 (28.6%)	37 (41.1%)	20 (20.6%)
Stage II or III	48 (48.0%)	16 (29.1%)	41 (42.3%)	33 (47.1%)	27 (30.0%)	39 (40.2%)
Stage IV	11 (11.0%)	5 (9.1%)	8 (8.2%)	0	1 (1.1%)	30 (30.9%)
Unknown	1 (1.0%)	9 (16.4%)	19 (19.6%)	8 (11.4%)	7 (7.8%)	2 (2.1%)
Mean 1st PFT (±SD)						
% predicted FVC	97.2 ±17.6	89.8 ±26.4	94.8 ±18.4	96.1 ±19.0	99.4 ±17.7	87.3 ±23.4
% predicted FEV1	89.9 ±18.2	82.2 ±25.3	86.0 ±19.4	87.0 ±23.4	91.7 ±19.6	77.8 ±22.4
% predicted DLCO	77.3 ±16.4	77.8 ±22.0	77.7 ±16.3	75.1 ±14.8	74.8 ±16.3	64.8 ±20.0

Osteoporosis

Few patients were diagnosed with osteoporosis or osteopenia (table 3). 11 (0.6%) out of 509 patients were diagnosed with osteoporosis and six (1.6%) out of 509 patients were diagnosed with osteopenia. Another six patients in whom a DEXA scan was performed had a normal T-score. It was not possible to provide an estimation on the feasibility for this outcome measure, for a number of reasons. First, it was not possible to identify those patients at risk of developing osteoporosis. Second, it was unclear which patients were monitored according to a locally available protocol on their bone health status. Third, we were unable to identify whether there was an active decision by the pulmonologist to not perform a DEXA scan.

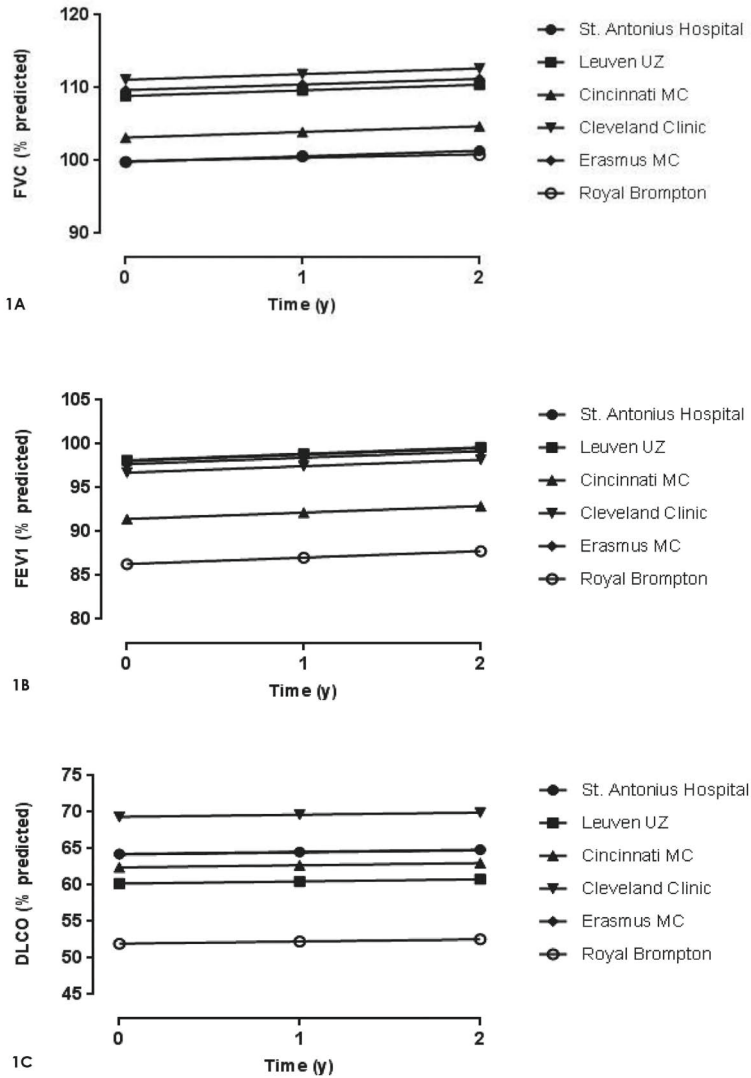


Figure 1A-C. Linear-mixed model pulmonary function parameters over time

All pulmonary function results are based on the EGKS reference equations.

In 1-A, the St. Antonius hospital and Leuven UZ follow and the Erasmus MC and Royal Brompton follow a similar trend. In 1-B, the St. Antonius hospital, Erasmus MC and Leuven UZ follow a similar trend. In 1-C, the St. Antonius hospital and the Erasmus MC follow a similar trend.

Predictions are plotted for white patients. For non-white patients the intercept (baseline) starts lower: -16.8 (1-A), -12.6 (1-B) and -11.4 (1-C) for each center. The trend follows the same line as presented above.

Linear-mixed model with fixed effects: time in study and ethnicity.

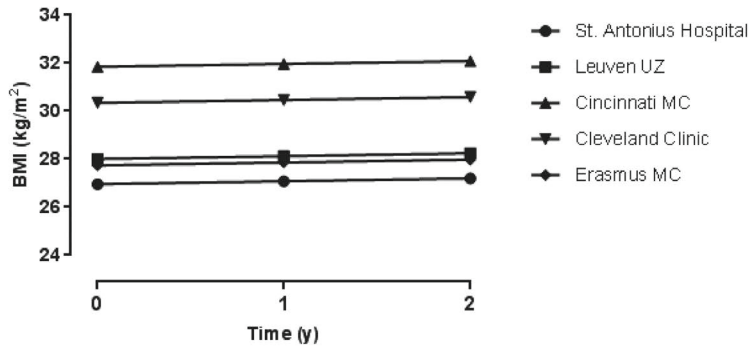


Figure 2. Linear-mixed model BMI over time

Linear-mixed model with fixed effects: time in study. The Royal Brompton hospital was not able to collect weight changes over time. BMI = body mass index.

Table 3. Outcome measures of the multicenter study cohort (n=509).

	St. Antonius (n=100)	Cincinnati MC (n=55)	Cleveland Clinic (n=97)	Erasmus MC (n=83)	Leuven UZ (n=90)	Royal Brompton (n=97)
Tier 1						
1. Mortality	0	1	0	0	1	4
Number of months between diagnosis and date when patient died (±SD)	0	56	0	0	42	32.3 ±27.6
2. Mean number of PFTs	5 ±3.0	1.7 ±0.9	3.6 ±2.5	4.6 ±3.3	5.4 ±4.2	3 ±1.6
3. sIL-2R						
Baseline sIL-2R (pg/ml)	5619 ±4099 (n=87)	nd	nd	nd	nd	nd
Tier 2						
4. Weight gain BMI changes	0.7	0.4	0.03	0.2	-0.1	0.2
Number of months between first/last BMI (±SD)	36.8 (±10.8)	15.6 (±16.9)	36.7 (±16.8)	41.4 (±15.5)	34.4 (±23.7)	24.4 (±8.0)
Tier 3						
5. Quality of Life	nd	nd	nd	nd	nd	nd
6. Osteoporosis						
Osteopenia	3 (3.0%)	1 (1.8%)	1 (1.0%)	0	1 (1.1%)	0
Osteoporosis	2 (2.0%)	3 (5.5%)	5 (5.2%)	1 (1.2%)	0	0
Normal T-score	4 (4.0%)	0	0	2 (2.4%)	0	0
7. Clinical Outcome Status						
COS 1-3	18 (18.0%)	2 (3.6%)	16 (16.5%)	7 (8.4%)	14 (15.5%)	3 (3.1%)
COS 4-6	26 (26.0%)	9 (16.4%)	10 (10.3%)	25 (30.1%)	28 (31.0%)	36 (37.1%)
COS 7-9	53 (53.0%)	44 (80.0%)	71 (73.2%)	51 (61.5%)	37 (41.2%)	54 (55.7%)
Unknown	3 (3.0%)	0	0	0	11 (12.3%)	4 (4.1%)

Clinical outcome status (COS)

COS was evaluated in all centers (table 3). Overall, out of the 509 patients where COS was evaluated, 310 (60.9%) patients were still requiring systemic therapy 2 years after the diagnosis. In this retrospective cohort, it was feasible to collect data internationally for this outcome measure (collected in 100% of patients).

Table 4. Pulmonary function changes between first and last measure.

	FVC % predicted (n=509)			p-value
	≥ -10% worsening	Between -10% / 10% change	≥ 10% improvement	
Patients (n, %)	50 (9.8)	352 (69.2)	107 (21.0)	
Mean FVC change (±SD)	-16.6 ±6.9	0.7 ±4.8	18.4 ±8.5	
Time between first-last PFT (months) (±SD)	37.0 ±16.8	31.1 ±17.7	34.4 ±17.4	0.035
Age at diagnosis (±SD)	48.9 ±10.6	46.9 ±11.7	45.5 ±12.2	0.231
Weight, kg (±SD)	88.4 ±20.7	85.4 ±19.6	83.6 ±22.7	0.399
	FEV1 % predicted (n=509)			p-value
	≥ -10% worsening	Between -10% / 10% change	≥ 10% improvement	
Patients (n, %)	44 (8.7)	357 (70.1)	108 (21.2)	
Mean FEV1 change (±SD)	-18.5 ±7.8	0.4 ±4.9	18.9 ±12.7	
Time between first-last PFT (months) (±SD)	40.5 ±16.8	31.0 ±17.6	33.7 ±17.3	0.002
Age at diagnosis (±SD)	48.3 ±11.6	47.0 ±11.3	45.6 ±12.7	0.383
Weight, kg (±SD)	91.0 ±19.3	84.2 ±20.1	86.5 ±21.5	0.100
	DLCO % predicted (n=492)			p-value
	≥ -10% worsening	Between -10% / 10% change	≥ 10% improvement	
Patients (n, %)	67 (13.6)	341 (69.3)	84 (17.1)	
Mean DLCO change (±SD)	-15.6 ±5.4	0.4 ±5.0	17.0 ±5.4	
Time between first-last PFT (months) (±SD)	35.2 ±16.7	31.6 ±16.9	36.6 ±18.4	0.029
Age at diagnosis (±SD)	49.5 ±11.8	47.1 ±11.4	43.4 ±12.0	0.004
Weight, kg (±SD)	86.3 ±20.1	84.8 ±19.8	86.2 ±23.7	0.769

p-values are based on ANOVA test.

DISCUSSION

In this study we present the results of the first evaluation of the standard set, previously developed for pulmonary sarcoidosis patients. We show that collecting data in a retrospective multicenter international cohort is feasible for the outcomes mortality, pulmonary function, weight changes and COS. Conversely, it is not (yet) feasible to collect data for international comparisons on QoL, sIL-2R and osteoporosis.

We developed a standard set for pulmonary sarcoidosis patients in 2015.[8] Until now, to our knowledge, there have been no scientific papers implementing and reflecting on a standard set for pulmonary sarcoidosis patients in a clinical setting. Although many standard sets for other conditions have been developed recently, real-world implementation of outcome measures and how they function in practice are lacking.[1] Our study provides information on the feasibility of implementing the pulmonary sarcoidosis standard set. We present the first results of a full standard set developed for pulmonary sarcoidosis patients in collaboration with six ILD centers from three different countries. Recruitment of the centers focused on specialized sarcoidosis centers, which potentially have differences in baseline clinical features and ethnicity. In addition, treatment was different between centers. Although several ILD clinics report on similar clinical outcomes such as spirometry and weight changes, globally there is little consensus which clinical outcomes should be reported on.[14] In order to realize the implementation of VBHC, it is important to know what the most important outcomes and their feasibility are to report on for RCTs as well as for quality of care oriented studies.

Based on our experience with the standard set for pulmonary sarcoidosis, it is feasible to implement some outcomes of the standard set in clinical practice. We do wish to critically reflect on the outcome measures and the potential to use the results as a basis for improving the quality of care.

Outcomes measures for pulmonary sarcoidosis

Tier 1 degree of health

Mortality

Mortality for pulmonary sarcoidosis is generally considered to be low, although there are subsets of patients, mainly those with extensive fibrotic lung disease and those with significant cardiac sarcoidosis, who experience markedly higher mortality rates than the general population.[15] Compared to Scadding stages I–III, patients with stage IV patients have a worse survival,[16] and evidence of fibrosis on chest computed tomography is an independent risk factor for higher mortality.[15,17]

It may be more meaningful and clinically relevant to use mortality as an outcome measure in the subgroup with pulmonary fibrosis on imaging.[16,17] Indeed, the highest number of deaths were observed at the Royal Brompton Hospital, where a significantly higher proportion of patients with stage IV disease were observed compared to the other centers. Especially for clinical trials, measuring mortality is feasible although not always a clinically

meaningful and relevant outcome in pulmonary sarcoidosis patients. In a subset of patients this might be more meaningful, such as in pulmonary fibrosis.

Lung function

As expected, due to variation in the patient composition of the cohorts, the six participating centers varied in baseline FVC. However, we did not find variation in the lung function trends over a period of 2 years between the six centers. Pulmonary sarcoidosis may cause significant airflow obstruction. However, we did not find significant differences between centers in FEV1 trend over time.[18] Other ILDs, such as idiopathic pulmonary fibrosis show a more progressive disease pattern with FVC worsening and high mortality rates over time. Nevertheless, pulmonary sarcoidosis is progressive in a subgroup of patients. We observed a tendency for an improvement over time for the three spirometry parameters. In a large (n=1774) cohort consisting of sarcoidosis patients, pulmonary function improved over time.[19] FVC has been recommended as the first-choice clinical end-point for pulmonary sarcoidosis trials [20], but FVC does not always accurately reflect the varying disease-related manifestations.[14] Looking at our own data, this outcome measure was not able to identify potential practice variation. In addition, over time FVC showed minor improvements. Therefore, it could be reconsidered whether this should be the outcome measure of first choice, also from the patient's perspective. A responder analysis could be useful in identifying the proportion of patients who benefit and in defining a responder cut-off.

sIL-2R

Based on analysis of the retrospective cohort consisting of 87 patients treated at the St Antonius Hospital, this biomarker was considered a possible feasible outcome measure in specific settings. In addition, it could potentially be used as a predictive biomarker, as we have shown that patients with elevated baseline sIL-2R levels are at risk of requiring therapy 2 years after the diagnosis. This may be confounded, as the treating physician may be less inclined to discontinue therapy in someone with higher baseline sIL-2R. Based on a review it was concluded that there are conflicting data concerning the correlation between changes in sIL-2R level and treatment effects such as PFT.[21] Therefore, the role of determining sIL-2R in clinical practice needs further research.

Looking at the total multicenter retrospective cohort, it is not feasible to collect data of this outcome measure. In the Dutch setting this might be feasible, as sIL-2R data was collected in 84% of the patients. This is also related to higher costs of the sIL-2R measurements in some of the centers.

Tier 2 disutility of care

BMI was a feasible parameter to collect (81%). No differences between centers were observed in BMI trends over time. It may be that with more prolonged periods of observation differences in trend over time would become apparent. BMI trends over time did not appear to differ between centers. However, for baseline BMI, we did see substantial differences. As weight gain is an important side-effect, often due to high-dose and long-term glucocorticoid use, this can be an important outcome measure to achieve improved quality of care in the future.[22] Additionally, prolonged high-dose glucocorticoid therapy is associated with a large number of negative side-effects, including weight gain, the development of osteoporosis and diabetes.[22]

Tier 3 long-term consequences of therapy

COS

Out of 509 patients, 310 (60.9%) patients were still requiring systemic therapy 2 years after the diagnosis. However, it was challenging to collect the COS data, as this is not a routinely reported outcome measure in electronic patient records. Pulmonologist and data managers had to read the patients' electronic record and make a judgement on the COS. Medical history data used to judge the patients' COS could create some individual variability in interpretation. When simplifying COS, there may be less interobserver variability in scoring the patients' COS. We therefore advise to simplify COS into three categories: 1) never treated (COS 1–3), 2) previously treated (COS 4–6) and 3) current therapy (COS 7–9). These main categories could also be used when performing a subgroup analysis.

Quality of Life (QoL)

Unfortunately, QoL was not yet routinely measured in any of the centers. Therefore, we are not able to evaluate the added value of collecting and comparing this outcome measure. Should centers wish to prioritize the implementation of patient-reported outcome measures, additional staffing is required, facilitating data collection.

Osteoporosis and Osteopenia

Glucocorticoids are considered first-line therapy for treating pulmonary sarcoidosis. Sarcoidosis patients may be treated with glucocorticoids for a long time, sometimes even for years. Long-term use of glucocorticoids can eventually increase the risk of developing osteoporosis.[23, 24] Untreated sarcoidosis has also been associated with low bone mineral density.[25] Moreover, corticosteroid use can cause increased bone resorption, decreased bone formation and lead to a net bone loss. In our retrospective cohort few patients were

diagnosed with osteopenia or osteoporosis. We believe this percentage may be too low and it is likely that this outcome was under-reported.

A significant dose–response relationship was observed between the cumulative dose of glucocorticoids and risk of any fracture.[26] In a retrospective cohort study of newly diagnosed sarcoidosis patients consisting of 105 patients ever treated with glucocorticoids (GC group), and 49 patients (no-GC group) not treated with glucocorticoids during a follow-up of 101 months, adverse consequences due to glucocorticoids therapy were evaluated.[22] In the GC group, 16 (15.2%) patients developed new osteoporosis or osteopenia. In the no-GC group, five (10.2%) patients developed osteoporosis or osteopenia. Therefore, this outcome measure is mainly of importance for long-term and high-dose glucocorticoids users.

Another reason for low numbers of osteoporosis and osteopenia can be due to the fact that referral centers performed a DEXA scan, but did not share the results. We were unable to evaluate the feasibility of this outcome measure. As earlier stressed, we were unable to identify those patients being at risk of developing osteopenia/osteoporosis in each center. It would be useful to develop an international standard for when to perform a DEXA scan.

Organizational Level

Healthcare systems are complex and there are large differences between healthcare systems globally, which can be a barrier to having valid international comparison of outcomes.[1] In order to have solid ongoing data collection, it is crucial to have a dedicated person in each center to manage the data collection process. Secondly, it is important that the team members have good understanding of how the outcome measures can be used. When there is good understanding of the potential of outcome measures, this can be used more effectively for quality improvement efforts or for the planning of future care.[27]

The objectives of clinical reporting include increasing (shared) decision making for patients and physicians, encourage quality improvement, better performance management and contributing to research.[28] When data and outcome measures are made public, this may promote improvement in care, as centers are more likely to discuss results and change practices. Thus, transparency can make physicians aware of practice variations and may help to improve care.

Limitations

First, although we were able to present data in an international multicenter initiative, our initiative represents only centers from the United States and three European countries.

There was no representation from Asia, Australasia, Africa or South America. International involvement is key in order to have good implementation of the standard outcome set. Hopefully in the future the standard set can be evaluated and validated as part of a larger international network of ILD clinics, for example, in a yearly evaluation cycle. However, for the Netherlands and the USA, we have reached a reasonable representation of ILD expert clinics. Two out of the three ILD expert centers in the Netherlands (officially declared by the Ministry of Health, Welfare and Sport) were part of the expert group.

Second, data were collected retrospectively. Patients visited the clinic at different time points, which makes it more difficult to evaluate and compare data. Furthermore, the centers measure and report some outcomes differently, such as ethnicity. In some centers ethnicity can only be evaluated based on photographs in the electronic patient record. Other centers report ethnicity only in two categories: Caucasian or non-Caucasian or Hispanic or non-Hispanic. Third, we were required to extract most of the data from the hospital databases manually, as an automated system for extracting these data in the respective centers does not currently exist. It was challenging to collect some of the required variables of the standard set, for example the COS data, as this information is not routinely reported. Fourth, underlying variation in routine daily clinical practice may exist due to differences in care pathways, but also due to costs between countries when measuring certain clinical outcome measures. Fifth, the definition of feasibility is strongly influenced by the number of patients being part of the cohort from each center. Sixth, we were unable to integrate QoL outcomes. The potential of routinely measuring QoL in daily clinical practice can be an outcome measure of great importance. It would be of great value if future trials more closely reflected on how systematically measuring QoL can enable improvements in the quality of care. Although some centers measure this, QoL is rarely being followed-up on a systematic basis.

Finally, we do not know whether this standard set is the most relevant from a patient's perspective. As stressed earlier, FVC is considered important for the follow-up of sarcoidosis. These are chosen for convenience and feasibility rather than this being the optimal standard set from a patient's perspective. Therefore, evaluating what patients consider to be the most important and relevant outcomes is key for future studies.

CONCLUSIONS

We have developed a standard set that can be used both retrospectively and prospectively to compare clinical outcomes of different sarcoidosis centers. The dataset can be improved by collecting this information prospectively over time. This set can support further

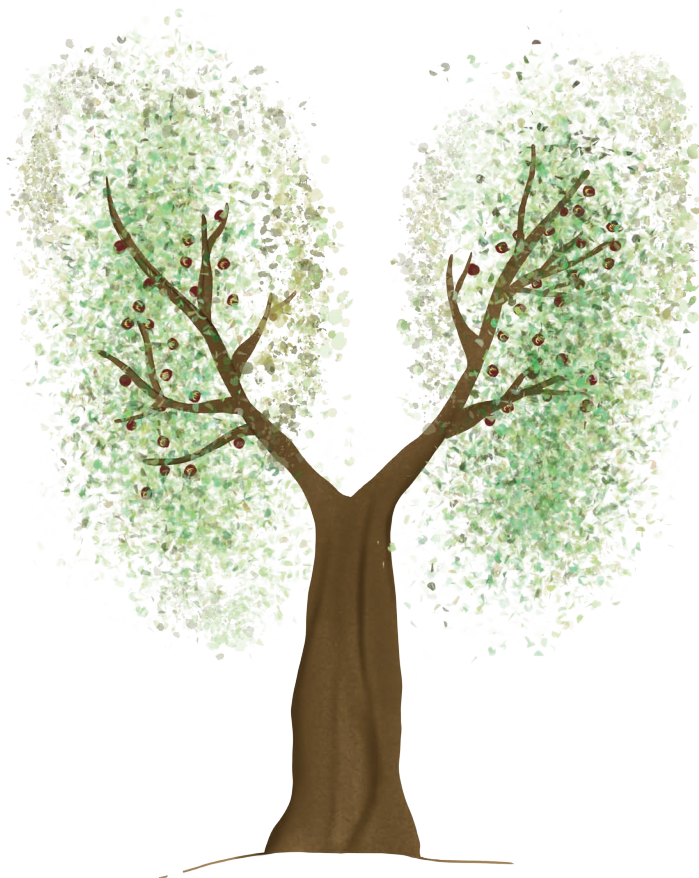
implementation of VBHC and the standardization of collecting outcomes for pulmonary sarcoidosis patients. Efforts on systematically measuring outcomes have the potential to create opportunities for improving treatment decision making and realize benchmarking between different healthcare systems, both on a regional and international level.

In conclusion, for international collection of a standard outcome set in pulmonary sarcoidosis, based on our definition that it was measured in >80% of the patients, this study showed that it is feasible to collect four out of seven outcome measures; data on mortality, changes in pulmonary function, changes in weight/BMI and the COS. It is not (yet) feasible to retrospectively collect data on sIL-2R, osteoporosis and QoL internationally.

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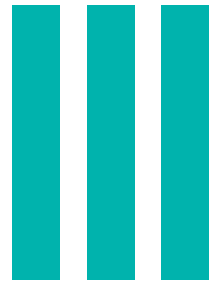
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Implementation of Best
Practice & Costs

Part





**Patterns of Healthcare
Resource Utilization in
Patients with Sarcoidosis: a
Cross-Sectional Study**

5

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ABSTRACT

Background: Limited data are available on healthcare resource use and costs in patients with sarcoidosis. The primary aim of this study was to describe cost-drivers of the top 1% and top ≥ 1 -5% high-cost patients with sarcoidosis. The secondary aim was to compare costs of patients with and without fatigue complaints and to compare comorbidities.

Methods: We conducted a retrospective observational cross-sectional study in 200 patients diagnosed with sarcoidosis. Hospital administrative databases were used to extract healthcare utilization on the individual patient level. Healthcare costs were categorized into nine groups.

Results: Average total health care costs for the top 1% (n=22), top ≥ 1 -5% (n=88) and bottom 95% beneficiaries (n=90) were € 108.296, €53.237 and €4.817, respectively. Mean treatment time in days for the top 1%, top ≥ 1 -5% and the random sample of the bottom 95% was 1688 days (± 225), 1412 days (± 367) and 775 days (± 659), respectively. Mean annual costs for the top 1%, top ≥ 1 -5% and the random sample of the bottom 95% are €51.082, €27.840 and €8.692, respectively. We identified three cost-drivers in the top 5% high-cost patients: 1) expensive medication, 2) intensive care and 3) costs made at the respiratory unit. Patients with and without fatigue showed to have comparable mean costs. High-cost patients were more likely to have multiple organs involved due to sarcoidosis.

Conclusions: We identified expensive medication as the main cost-driver in the top 5% high-cost patients with sarcoidosis. The study findings can help to tailor interventions for improving the quality of care and reducing overall costs.

INTRODUCTION

Sarcoidosis is a chronic granulomatous disease characterized by persistent body complaints in multiple organs and patients suffer from a broad range of nonspecific symptoms.[1–4] The inflammation level as well as organs affected are highly variable. In more than 90% of the cases, sarcoidosis affects the lungs. Health-related quality of life (HRQoL) and health status is often reduced in patients with sarcoidosis.[5–8] Fatigue is an often reported symptom in patients with sarcoidosis.[2, 9, 10] In a sample of 1197 patients with sarcoidosis, 70% of the patients reported fatigue as a feature of their sarcoidosis.[10]

Detailed insights into the costs of patients with advanced sarcoidosis are however lacking. Efforts to further improve the quality of care could specifically target advanced sarcoidosis patients. Therefore, it would be useful to have a detailed picture of high-cost patients with sarcoidosis which can enable better evaluation of the current treatment choices.

The most complex patient group is that with the highest costs and needs, with a variety of complex medical conditions. About 5% of patients with various conditions account for 50% of the total healthcare spending.[11] Detailed insight into the disease specific costs regarding patients with sarcoidosis are getting more attention in the literature, although this is still limited.[12–14] Previous research has demonstrated that the cost distribution for patients with sarcoidosis is highly skewed. High-cost patients had more sarcoidosis related comorbidities compared to low-cost patients.[12–14] Previous research has shown commercial payers in the USA incurred a mean of \$19,714 total annual healthcare costs per sarcoidosis patient.[12] It was furthermore reported that the main cost drivers identified were outpatient visits (46% of the costs) and inpatient admissions (32% of the costs). Mean healthcare costs in a US-based patient group in the top quintile were \$73,346. The authors furthermore concluded that this subgroup of most costly patients with sarcoidosis might be worthwhile to invest in concerning outcome improvement efforts. Another study, based on a U.S. national healthcare database, found that the median healthcare costs were \$18,663 for patients with sarcoidosis per year.[14] The top 5% costliest patients with sarcoidosis exceeded \$90,000 per year. However, little is known on the healthcare utilization and patient characteristics of high-cost patients with sarcoidosis. Furthermore, no other studies have tried to identify cost drivers in this high-cost patient subgroup and identify their patient characteristics in a (Dutch) cohort. This can be valuable as it will enable to assess the effectiveness of current treatment choices. Therefore, the primary aim of this study was to describe cost-drivers of the top 1% and top ≥ 1 -5% high-cost patients with sarcoidosis. The secondary aim was to compare costs of patients with and without fatigue complaints and to compare comorbidities.

METHODS

Design and context

This study was a cross-sectional study using internal data of patients with sarcoidosis who visited the St. Antonius Hospital in the Netherlands. The study used administrative data provided by the business intelligence unit of the St. Antonius hospital. Patients were treated in the St. Antonius Hospital between January 1st 2011 and January 1st 2016. In total, 2251 patients with sarcoidosis were identified, from which 200 patients were used for the final analysis.

We examined healthcare costs and identify the beneficiaries within the top 1% and the top $\geq 1\%$ –5% of total costs.[16] The 2251 patients from our cohort were ranked in total costs after which the top 1% (0-0.99) and the $\geq 1\%$ –5% (1.0-4.99) most expensive patients were identified (n=110). From the remaining 2141 patients, a random sample of 90 patients was selected. Thus, from the total cohort, additional data was collected for 200 patients in total. Patients in the top 5% (so the top 1% and the top $\geq 1\%$ –5% together) of total healthcare costs were defined as high-cost patients.

Data collection

Baseline patient characteristics were examined for all patients with sarcoidosis (n=200). Patient characteristics included age, gender, BMI, Scadding stage, survival, fatigue, treatment time and the year of the diagnosis. Furthermore we collected information regarding the sarcoidosis related organ involvement (pulmonary, cardiac and neurologic). In addition, we collected data on whether or not patients suffered from pulmonary hypertension and obstructive sleep apnea (OSAS).

Mean treatment time was defined as the first date of receiving treatment minus the last date of receiving treatment at the St. Antonius hospital between January 1st 2011 and January 1st 2016. When the patient reported to experienced fatigue more than three times during the outpatient visits, he/she was seen as a patient with fatigue complaints in the analysis.

Healthcare utilization and cost calculation

Hospital administrative databases were extracted for all healthcare utilization as part of the diagnosis code for sarcoidosis patients. Next, this was grouped into six categories: 1) expensive medication (infliximab, adalimumab and rituximab), 2) intensive care/general ward nursing 3) respiratory medicine, 4) clinical chemistry, 5) radiology/ nuclear medicine, and 6) other.

Total costs per patient were calculated by summing the number of resources used multiplied by the costs per resource. Total annual costs were calculated by summing up the costs of all individual months the patient received care and subsequently correcting for the number of months. Months when no care was delivered were disregarded. Total costs per resource item were based on the national diagnosis treatment combination rates as defined in 2015 by the St. Antonius hospital. Costs of drugs were based on the lowest reported drug price according to the information of the Healthcare Institute of the Netherlands valued in 2019. Total drug costs per patient were calculated using the amount of drugs (in mg) used multiplied with the price per mg in Euros.

Analyses

Descriptive statistics were used to present total costs. Costs were expressed as mean and interquartile range (IQR) due to skewness of the data. Overall mean costs (IQR) were presented for total healthcare costs made between January 2011 and January 2016. Treatment time and time between diagnosis/first visit were expressed as mean (\pm SD). All categorical data were presented in *n* and percentage (%). All analyses were performed in SPSS (IBM SPSS Statistics version 24).

RESULTS

For the 200 patients analyzed, average total healthcare costs for the top 1%, top \geq 1%–5% and bottom 95% beneficiaries were €108.296, €53.237 and €4.817, respectively. The mean annual cost are €51.082, €27.840 and €8.692, respectively. Mean treatment time in days for the top 1%, top \geq 1–5% and the random sample was 1688 days (\pm 225), 1412 days (\pm 367) and 775 days (\pm 659), respectively. Table 1 presents the demographics of the study population. In all groups, males were overrepresented, especially in the top 1%, where 68.2% of the patients were male. Mean age at diagnosis was comparable between the groups. In Table 2, the demographics are presented for the patients with less advanced sarcoidosis (without cardiac sarcoidosis, neurosarcoidosis or pulmonary hypertension). Here, top 1% beneficiaries were much older than the top \geq 1–5% and the random sample of the bottom 95%. Furthermore, mortality was higher for high-cost patients, as 18% in the top 1% and 9.1% in the top \geq 1%–5% died. In the random sample of the bottom 95%, 2.2% of the patients died.

Association of fatigue

In the top 1% and top \geq 1%–5% 81.8% and 75% showed the experience fatigue complaints, respectively. In the random sample of the bottom 95%, 38.9% showed to have fatigue complaints.

In Table 3 the mean costs and patient characteristics are presented for patients with and without fatigue complaints for two groups: for the top 5% (the top 1% and top $\geq 1\%$ -5% together) and for the random sample of the bottom 95%. Patients with and without fatigue showed to have comparable mean costs. Average total costs for the top 5% patients with fatigue were €65.512 and €60.165 without fatigue complaints. Average annual costs for the top 5% patients with fatigue were €33.039 and €30.311 without fatigue complaints. For the random sample of the bottom 95%, average total costs for patients with fatigue was €6.546 for patients with fatigue complaints and €3.716 for patients without fatigue complaints. In both the top 5% and random sample of the bottom 95%, patients with fatigue complaints were more likely to have pulmonary sarcoidosis, pulmonary hypertension, cardiac sarcoidosis, neurosarcoidosis and OSAS.

Table 1. Patient characteristics for three cost groups.

Patient characteristics	Top 1% (n=22)	Top $\geq 1\%$ -5% (n=88)	Sample of bottom 95% (n=90)
Male (n, %)	15 (68.2%)	52 (59.1%)	51 (56.7%)
Age at diagnosis (mean, \pm SD)	44 \pm 12.3	43 \pm 11.0	45 \pm 12.6
Mean costs (€, IQR)	€108.296 (€25.497)	€53.237 (€39.384)	€4.817 (€4.466)
Mean annual costs (€, IQR)	€51.082 (€24.366)	€27.840 (€21.253)	€8.692 9 (€8.825)
Treatment time in days (\pm SD)	1688 \pm 225	1412 \pm 367	775 \pm 659
Time between diagnosis/first visit in years (\pm SD)	8.8 \pm 6.2	7.3 \pm 6.7	6.1 \pm 9.1
BMI (\pm SD)	32.0 \pm 7.1	27.8 \pm 4.7	29.1 \pm 5.9
Fatigue (n, %)	18 (81.8%)	66 (75.0%)	35 (38.9%)
Deceased (n, %)	4 (18%)	8 (9.1%)	2 (2.2%)
Pulmonary sarcoidosis (n, %)	20 (90.9%)	81 (92.0%)	56 (62.2%)
Pulmonary hypertension (n, %)	3 (13.6%)	9 (10.2%)	2 (1.7%)
Cardiac sarcoidosis (n, %)	2 (9.1%)	10 (11.3%)	5 (5.6%)
OSAS (n, %)	7 (31.8%)	9 (10.2%)	14 (15.6%)
Neurosarcoidosis (n, %)	6 (27.3%)	19 (21.6%)	12 (13.3%)
Scadding stage (n, %)			
Scadding 0	4 (18.2%)	16 (18.2)	0 (0%)
Scadding I	2 (9.1%)	13 (14.8%)	19 (21.1%)
Scadding II	6 (27.3%)	18 (20.5%)	15 (16.7%)
Scadding III	4 (18.0%)	13 (14.8%)	4 (3.0%)
Scadding IIII	4 (18.0%)	28 (31.8%)	13 (14.4%)

IQR= Inter quartile range.

Comorbidities

In the top 1% and the top $\geq 1-5\%$ there was more organ involvement of sarcoidosis compared to random sample of the bottom 95%. Cardiac and pulmonary sarcoidosis and neurosarcoidosis were more likely in the top 1% and top $\geq 1-5\%$. OSAS was more present in the top 1% compared to the random sample of the bottom 95% (31.8% versus 15.6%). When patients with cardiac sarcoidosis, neurosarcoidosis or pulmonary hypertension were excluded, OSAS was still more present in the top 1% of the patients compared to both the top $\geq 1-5\%$ and the random sample of the bottom 95% (33% versus 5% and 10%, respectively).

Table 2. Patient characteristics for three cost groups (without cardiac sarcoidosis, neurosarcoidosis and pulmonary hypertension).

Patient characteristics*	Sample of bottom		
	Top 1% (n=12)	Top $\geq 1-5\%$ (n=51)	95% (n=70)
Male (n, %)	8 (66.7%)	31 (60.8%)	39 (55.7%)
Age (mean, \pm SD)	47 \pm 14.3	41 \pm 11.0	44 \pm 12.1
Mean total costs (€, IQR)	€107.970 (€24.064)	€50.861 (€45.551)	€4.184 (€3.844)
Mean annual costs (€, IQR)	€50.837 (€22.245)	€25.322 (€17.413)	€9.472 (€10.307)
Treatment time in days (\pm SD)	1716 \pm 243	1411 \pm 352	700 \pm 650
Time between diagnosis/first visit in years (\pm SD)	7.9 \pm 7.8	7.3 \pm 5.7	5.9 \pm 9
BMI (\pm SD)	33.8 \pm 6.9	27.0 \pm 4.0	28.7 \pm 4.9
Fatigue (n, %)	10 (83.3%)	35 (68.6%)	21 (30%)
Deceased (n, %)	2 (16.7%)	5 (9.8%)	0 (0.0%)
Pulmonary sarcoidosis (n, %)	11 (91.7%)	47 (92.2%)	44 (62.9%)
OSAS (n, %)	4 (33.0%)	3 (5.0%)	7 (10.0%)
Scadding stage (n, %)			
Scadding 0	2 (16.7%)	7 (13.7%)	5 (7.1%)
Scadding I	0 (0.0%)	5 (9.8%)	14 (20.0%)
Scadding II	3 (25.0%)	13 (25.5%)	15 (21.4%)
Scadding III	3 (25.0%)	9 (17.6%)	4 (5.7%)
Scadding IIII	4 (33.3%)	17 (33.3%)	9 (12.9%)
Unknown	0	0	23 (32.9%)

IQR= Inter quartile range. *without cardiac sarcoidosis, neurosarcoidosis and pulmonary hypertension.

Table 3. Patient characteristics for patients with and without fatigue.

Patient characteristics	Top 0-5%		Random sample	
	With fatigue (n=84)	Without fatigue (n=26)	With fatigue (n=35)	Without fatigue (n=55)
Male (n, %)	49 (58.3%)	18 (69.2%)	15 (42.9%)	5 (9.1%)
Age (mean \pm SD)	53 (\pm 11.1)	48 (\pm 9.0)	51 (\pm 12.5)	52 (\pm 11.5)
Mean costs (€, IQR)	€65.512 (€44.486)	€60.165 (€54.307)	€6.546 (€6.080)	€3.716 (€2.552)
Mean annual costs (€, IQR)	€33.039 (€22.439)	€30.311 (€35.966)	€10.129 (€8.479)	€7.704 (€10.068)
Treatment time in days (\pm SD)	1484 (\pm 347)	1410 (\pm 401)	978 (\pm 679)	634 (\pm 613)
Time between diagnosis/first visit in years (\pm SD)	7.4 (\pm 6.8)	8.3 (\pm 5.7)	6.9 (\pm 9.1)	5.6 (\pm 9.0)
BMI (\pm SD)	28.7 (\pm 5.3)	28.6 (\pm 6.2)	29.7 (\pm 6.8)	28.6 (\pm 5.2)
Deceased (n, %)	10 (11.9%)	2 (7.7%)	1 (52.9%)	0 (0%)
Pulmonary sarcoidosis (n, %)	78 (92.9%)	23 (88.5%)	24 (68.6%)	32 (58.2%)
Pulmonary hypertension(n, %)	10 (11.9%)	2 (7.7%)	2 (5.7%)	1 (1.8%)
Cardiac sarcoidosis (n, %)	10 (11.9%)	2 (7.7%)	4 (11.4%)	6 (10.9%)
OSAS (n, %)	16 (19.0%)	0 (0%)	8 (22.9%)	0 (0%)
Neurosarcoidosis (n, %)	22 (26.2%)	3 (11.5%)	7 (20.0%)	5 (9.1%)
Scadding stage (n, %)				
Scadding III	13 (15.5%)	4 (15.4%)	2 (5.7%)	2 (3.6%)
Scadding IV	23 (27.4%)	11 (42.3%)	7 (20.0%)	6 (10.9%)

IQR= Inter quartile range.

Cost-driver profile

The top 1% (n=22) spent a total of €3824 thousand. The top \geq 1-5% patients (n=88) spent a total of €6,809,799. Figure 1A-C presents the share per category in the total costs. The top 3 cost-drivers identified in both the top 1% and top \geq 1-5% high-cost patients were: 1) expensive medication, 2) intensive care/general ward nursing, and 3) costs made at the respiratory medicine department. Finally, the random sample of the bottom 95% spent a total of €442,019. Expenses made at the respiratory medicine department was the main cost driver. Within the cost for expensive medication, infliximab accounted for 83% of the costs in the top 1%. In the top \geq 1-5% this was 80% and in the random sample this was 98%. Adalimumab accounted for 16%, 19% and 0% of the total costs for expensive medication, respectively.

Table 4. Patient characteristics for patients with and without fatigue (without cardiac sarcoidosis, neurosarcoidosis and pulmonary hypertension).

Patient characteristics	Top ≥1-5%		Random sample	
	With fatigue (n=45)	Without fatigue (n=18)	With fatigue (n=21)	Without fatigue (n=49)
Male (n, %)	27 (60%)	12 (66.7%)	8 (38.1%)	31 (63.3%)
Age (mean, ±SD)	52 (±12.1)	48 (±8.9)	47 (±11.9)	52 (±11.4)
Mean costs (€, IQR)	€65.044 (€46.618)	€53.476 (€48.151)	€6.103 (€3.361)	€3.361 (€5.632)
Mean annual costs (€, IQR)	€31.220 (€23.170)	€26.497 (€24.401)	€12.787 (€10.036)	€7.893 (€10.890)
Treatment time in days (±SD)	1502 (±326)	1387 (±414)	896 (±683)	609 (±621)
Time between diagnosis/first visit in years (±SD)	6.7 (±6.0)	9.1 (±6.1)	6.0 (±8.2)	5.9 (±9.4)
BMI (±SD)	28.9 (±5.3)	27.0 (±5.3)	28.5 (±4.6)	28.8 (±5.1)
Deceased (n, %)	5 (11.1%)	2 (11.1%)	0 (0%)	0 (0%)
Pulmonary sarcoidosis (n, %)	42 (93.3%)	16 (88.9%)	15 (71.4%)	29 (59.2%)
OSAS (n, %)	7 (15.6%)	0 (0%)	3 (14.3%)	4 (8.2%)
Scadding stage (n, %)				
Scadding III	8 (17.8%)	4 (22.2%)	2 (9.5%)	2 (4.1%)
Scadding IV	13 (28.9%)	8 (44.4%)	4 (19%)	5 (10.2%)

IQR= Inter quartile range. *without cardiac sarcoidosis, neurosarcoidosis and pulmonary hypertension.

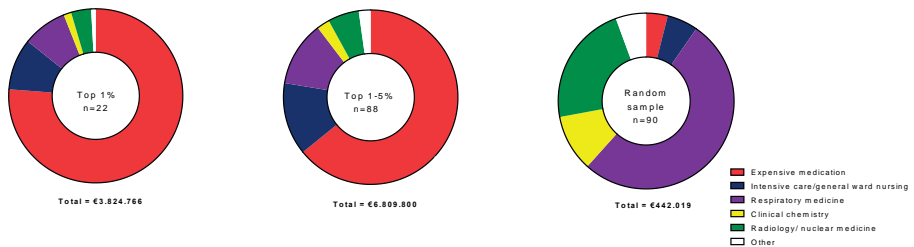


Figure 1. Distribution of costs by resource categories for the top 1%, top ≥1-5% high-cost patients and the low-cost random sample.

DISCUSSION

In this study, we provide cost-related information and describe characteristics of 200 patients with sarcoidosis in a Dutch patient cohort using administrative data. The healthcare cost distribution for patients with sarcoidosis are highly skewed. The average healthcare costs of the top 1% patients with sarcoidosis were 22 times higher compared to that of the random sample of the bottom 95% (€108.296 vs. €4.817, respectively). The mean annual healthcare costs of the top 1% patients with sarcoidosis were six times higher compared to that of the random sample of the bottom 95% (€51.082 vs. €8.692, respectively). Treatment time of the most expensive 1% was 2.5 times longer compared to the random sample. The top 1% patients and top ≥ 1 -5% patient showed to have more sarcoidosis related organ involvement compared to the random sample of the bottom 95%, indicating those are patients with more advanced sarcoidosis. Unexpectedly, patients with and without fatigue showed to have comparable mean costs and mean annual costs.

Although methodology and the data source used differ, our findings are consistent with other manuscripts studying the costs in patients with sarcoidosis.[12–14] Moreover, one study showed that patients in the top 5% in terms of costs, spent \$93,201.[14] Another study showed that the mean annual healthcare costs for patients in the top quintile were \$73,346 (based on 2015 data).[13] This was 10 times greater compared to the mean annual healthcare costs for the remaining patients. Further, to our knowledge, this is the first study to use such data to characterize high-cost patients with sarcoidosis and identify key drivers that contribute to costs in this patient population.

This study has a number of limitations. First, we have studied a group of patients visiting our center for a period of 5 year. Thus, total costs for the full treatment time per patient are not presented in this study. Moreover, it would have been interesting to see total costs over a full treatment period per patient and next, to identify the most expensive treatment period looking at the patient cohort. Secondly, we were unable to include the societal costs. This includes cost lost due to work loss of patients not being able to work due to the severity of their disease course. Thirdly, this study was based on a population in the Netherlands. Therefore, this information cannot be generalized to other populations where cost of healthcare utilization can be very different. Also, some treatment options can be more expensive in other countries. It is known that performing a PET scan is more expensive in the USA compared to the Netherlands. As a consequence, the PET scan is performed less often in the USA. If we would leave out the PET scan cost, there would be no major changes in the cost distribution presented in Figure 1. Finally, a limitation with using annual costs is that we only used costs when care was delivered on a monthly basis.

So when a patient would come back after six months for follow-up, the months in between visits were not part of our annual costs definition.

CONCLUSIONS

In conclusion, this study found that high-cost patients with sarcoidosis were patients with higher rates of comorbidities and had increased use of healthcare resources. Specifically, they were more often in need of expensive medication for their treatment. Both the management as well as physicians can specifically use this information to realize improvements in the quality of care and reducing overall costs for patients diagnosed with sarcoidosis, especially in referral centers of excellence. Efforts to further improve the quality of care and clinical outcomes for patients with sarcoidosis could specifically target the most expensive patients, which can potentially reduce the overall costs.

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Outcomes in Pulmonary
Sarcoidosis: Results of
a Newly Implemented
Prednisone Protocol

6

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ABSTRACT

Background: Prednisone is used as first-line therapy for patients with pulmonary sarcoidosis. There is however no clear association between prednisone dose and FVC change in patients with pulmonary sarcoidosis. In order to improve our standard of care we introduced a more conservative prednisone protocol.

Methods: This study is a single center observational study, applying value-based healthcare (VBHC) and quality improvement (QI) principles. Prednisone intake was reduced from a starting dose of 40 mg to a starting dose of 20 mg. Primary outcomes evaluated were FVC, FEV1 and DLCO % predicted. The secondary outcome measure was BMI.

Results: 369 patients were included in the old-cohort and 215 in the new-cohort. In the old-cohort, 182 (49.0%) of the patients were treated with prednisone. In total, 114 patients (62.6%) were treated according to the old protocol with a mean initial prednisone dose of 32.1 ± 14.2 mg. In the new-cohort, 93 patients (45.0%) were treated with prednisone of which 53 patients (57.0%) received prednisone according to the new protocol. The mean initial prednisone dose in the new-cohort was 21.4 ± 9.8 mg. Changes in FVC and FEV1 % predicted did not vary. Change in % predicted DLCO was 2.4 ± 9.3 for the old-cohort and -1.3 ± 11.4 for the new-cohort ($p = 0.01$). No statistically significant changes in BMI were observed.

Conclusions: Our results indicate that in more than half of the patients the new protocol was followed. Data support the observation that a more conservative prednisone regimen might be equally effective, looking at changes in pulmonary function and BMI.

INTRODUCTION

Previously, a standard set for measuring and comparing outcomes over time was developed for patients with pulmonary sarcoidosis.[1] Furthermore, the set has been evaluated on its feasibility and to assess whether changes in outcomes between centers were observed.[2] In the literature, several standard sets have been developed applying value-based healthcare (VBHC).[3–6] One of the aims of VBHC is to measure clinical outcomes relevant for a specific patient group divided by the costs.[7] However, efforts in applying these sets and the actual use of clinical outcomes to identify quality improvement (QI) initiatives are lacking.[8]

Sarcoidosis is a multisystem disease which is histologically characterized by granulomatous inflammations.[9] In 90% of the cases the lungs are affected. The first-line therapy option for patients with pulmonary sarcoidosis remains prednisone.[9–11] The aim of therapy should be the treatment of inflammation and prevention of further deterioration of any organ damage and improving the quality of life, while avoiding negative side-effects such as weight gain.[12–14, 27] Prednisone remains the first-line pharmacological treatment option for patients with pulmonary sarcoidosis. Prednisone effectively reduces systemic inflammation in most people, stopping and/or preventing further organ damage. Although prednisone treatment in patients with pulmonary sarcoidosis is reported to induce short-term benefits concerning the inflammation level, the balance between dosage level and adverse side effects remains unclear.[11] Evidence for the most optimal prednisone treatment regimen is lacking. Protocols vary both nationally and internationally in prednisone dosage and tapering schemes. The suggested initial prednisone dose varies between 20-40 mg.[9]

A study evaluating what dosing strategy has the best balance between effect on pulmonary function and side-effects showed there was no clear association between prednisone dose and FVC change in newly-treated patients with pulmonary sarcoidosis.[15] Weight gain on the other hand was correlated with cumulative prednisone dose. Long-term and high-dose prednisone therapy is associated with a large number of side-effects impacting patients' quality of life, such as weight gain, diabetes, mood swings and osteoporosis.[14,16] Given the adverse effects of corticosteroids and the lack of studies evaluating the most optimal dosage regimen, it is advised to lower patients' initial prednisone dose and realize faster tapering.[14,15] However, it is unknown how this new regimen impacts patients' pulmonary function test (PFT) results and BMI. Therefore, we aimed to evaluate the effectiveness of a newly developed prednisone protocol that was implemented in September 2017 at the St. Antonius hospital. We looked at how the new prednisone doses scheme affected patients' pulmonary function and weight over time.

METHODS

Study structure and design

This study is a single center observational study, performed at the St. Antonius hospital in Nieuwegein, the Netherlands. The protocol for prednisone treatment was selected as an intervention after seven team meetings by the quality improvement team. In Table 1 more information is provided what was discussed during the meetings. This quality improvement team consisted of five team members including pulmonologists (n=2) and researchers (n=3). The final decision of the intervention was discussed with a specialized nurse from the interstitial lung disease (ILD) unit. After the intervention was selected, this was presented to the team of ILD nurses and one dietician. In Table 1, a full timeline is provided of the implementation process. We evaluated the implementation process of the QI project comparing it with the steps as described by the Implementation of Change Model (ICM). [17] The ICM has been used successfully in the process of implementing improvement initiatives.[18]

Quality improvement process

During the quality improvement process, the outcome data of the earlier developed standard set for patients with pulmonary sarcoidosis were discussed.[1,2] During the seven meetings with the quality improvement team, the plan-do-study-act (PDSA) method was used as a tool to guide the process.[19] During the meetings, we discussed the outcome data and went through the following three questions: What do we want to accomplish? What outcomes do we wish to improve? What changes can we make that can potentially lead to an improvement?[19]

One of the quality improvement team members facilitated and prepared the presentations and meetings. After each session, additional data analyses were needed until we reached consensus concerning the final quality improvement initiative.

Prednisone protocol

The new prednisone protocol was active since the first of September 2017. The old scheme was re-evaluated after insights from the literature and previous outcomes.[15] Differences between the old and new protocol were the initial prednisone dose of 40 mg and 20 mg, respectively. In addition, a consequent lower prednisone dose throughout the treatment was advised in the new protocol (Table 2). As for the old and new protocol, the protocol is used as guidance and allows for deviation. In the new protocol, it was advised that patients would not start on prednisone when: 1) patients had a BMI ≥ 25 ; 2) patients were diagnosed with diabetes mellitus; 3) patients were known with pseudo-resistant hypertension or 4) when patients were diagnosed with osteoporosis. Reasons to stop

prednisone therapy would be: 1) limited response to prednisone (persistent activity); 2) weight gain of > 5% of initial weight before the patient started with prednisone; 3) the patient developed steroid-induced DM/hypertension or osteoporosis or 4) due to other side-effects (e.g. insomnia, mood swings, etc.).

If it concerned a patient who was being referred to us and prednisone was started elsewhere (often higher dosage), the information of the therapy starting at our clinic was used. If e.g. a referral patient was switched to 2nd and/or 3rd line therapy or a tapering scheme was initiated by the pulmonologist, the patient was considered as being treated according to the (new) protocol. In case of serious organ threat, methylprednisone was chosen, followed by the lower prednisone schedule.

Measures and outcomes

For this study, the main outcome measures were pulmonary function test (PFT) results and weight change over time. Specifically, we aimed to observe whether changes in forced vital capacity (FVC) % predicted, forced expiratory volume in 1 second (FEV1) % predicted, diffusing capacity of the lung for carbon monoxide (DLCO) % predicted and weight occurred after the new protocol was initiated. Secondly, we wanted to compare the mean initial dosage of prednisone before and after the initiation of the protocol. In addition, we aimed to study in how many patients the protocol was being followed when receiving treatment with prednisone. Medical records were reviewed for diagnostic data, demographics, weight, pulmonary function parameters, and initial prednisone dose. The minimum clinically important difference (MCID) margin for % predicted FVC, FEV1 and DLCO was defined as when there was more than a 10% worsening in PFT compared to the before-cohort. All patients provided informed consent as part of the overall biobank policy. This is a broader informed consent form where patients agree their medical data and biobank material are being used for scientific purposes.

Patient and public involvement

Patients and the public were not involved in the design of the study. During a research meeting, data and the idea to adjust the prednisone protocol was presented to a patient representative. The patient did not comment on the manuscript.

Statistical analysis

The comparison of means of continuous variables was tested with the student t-test. Next, a Mann-Whitney U test or Chi-square test was performed. FVC, FEV1 and DLCO is shown as mean percent (%) predicted (\pm standard deviation (SD)) or as mean absolute change of % predicted (\pm SD) compared to baseline. All pulmonary function results are based on the European Community for Steel and Coal reference equations.[20]

Weight is shown as mean kg (\pm SD) or as mean absolute change (\pm SD) in kg compared to baseline. Prednisone dose is shown as mean daily dose in mg. All analyses were performed in SPSS (IBM SPSS Statistics version 24). A p-value of <0.05 was considered statistically significant.

Table 1. Implementation process and steps by the Implementation of Change Model (ICM).

Step of the Implementation of Change Model	Date	Description of the process
1. Development of proposal for change	December 2016 - May 2017	Based on outcome data of the standard set developed for pulmonary sarcoidosis patients, 7 meetings of 1 hour were organized with the quality improvement team in order to critically look at the data. The quality improvement team consisted of two pulmonologists, two senior researchers and one PhD student. Based on insights from 6 centers and 509 patients, baseline BMI values differed between centers. Specifically for our own center we have looked at the patients with long term prednisone use (≥ 2 years) and the change of BMI over time. We found that these patients had a higher BMI and that their BMI increased more compared to patients using prednisone for a shorter time, which is also known from the literature. As weight gain is experienced as a burden for patients, we wanted to minimize this and wanted to impact the patients weight changes over time.
2. Analysis of actual performance, targets for change	December 2016 - May 2017	We analyzed the following data: 1) Mortality 2) Changes in pulmonary function (forced vital capacity (FVC), forced expiratory volume in 1 s, diffusing capacity of the lung for carbon monoxide) 3) Soluble interleukin-2 receptor (sIL-2R) change 4) Weight changes 5) Quality-of-life (QoL) measures 6) Osteoporosis 7) Clinical outcome status (COS) In addition we have looked at prednisone use for only the St. Antonius hospital. Our targets for change were prednisone dosage and BMI change.
3. Problem analysis of target group and setting	June 2017 - August 2017	We organized a meeting with a specialized nurse to present data and the rationale for the after protocol. A presentation was given to nurses, dieticians after protocol and get their input.
4. Development and selection of strategies and measures to change practice	August 2017 - September 2019	An email was sent to all pulmonologists and residents with the information when the new protocol would be launched. A pulmonologist from the quality improvement team made sure that during the multi-disciplinary team meeting, the protocol would be guiding the treatment choices.
5. Development, testing and execution of implementation plan	May 2017 - August 2017	We developed the implementation plan. The quality improvement team was involved as well a nurse from the ILD unit. In the implementation plan we explained the rationale, objectives implementation actions and the analysis plan. The implementation plan was presented to the ILD nurses by the PhD student.

Table 1. Continued.

Step of the Implementation of Change Model	Date	Description of the process
6. Integration of changes in routine care	1 st of September 2017	No pilot phase was integrated as this concerned the change of a protocol for prednisone treatment for routine care. An email was sent to all pulmonologists and residents with the information of the new prednisone protocol and the date was announced when the protocol would be active. A pulmonologist from the quality improvement team made sure that during the multidisciplinary team meetings the protocol would be used as guidance for the treatment of patients with pulmonary sarcoidosis.
7. (Continuous) evaluation and (where necessary) adapting plan	September 2019 - March 2020	The protocol was evaluated 2 years after the protocol was implemented, as this time span would have sufficient number of patients in order to look at the effect on outcomes (pulmonary function, BMI and initial prednisone dose). No adjustments were made in the protocol after this was launched on September 1 st 2017.

Steps of the ICM adapted from Grol & Wensing (2013)[26]

6

Table 2. Doses regimen prednisone.

Old doses regimen	New doses regimen
• 4 weeks 40 mg/day	• 3 weeks 20 mg/day
• 4 weeks 30 mg/day	• 3 weeks 17,5 mg/day
• 4 weeks 20 mg/day	• 3 weeks 15 mg/day
• 2,5 mg per 4 weeks until maintenance dose of 10 mg/day	• 3 weeks 12,5 mg/day • Maintenance dose of 10 mg/day

RESULTS

Description of the cohorts

A total of 369 patients were included in the old-cohort and 215 patients in the new-cohort. First mean % predicted FVC was 96.9 ± 19.5 in the old-cohort and 98.3 ± 18.8 in the new-cohort. First mean % predicted FEV1 was 88.5 ± 21.1 in the old-cohort and 89.0 ± 20.4 in the new-cohort. Mean % predicted DLCO was 74.8 ± 16.2 for the old-cohort and 77.9 ± 18.7 ($p = 0.01$) for the new-cohort (Table 3). Average body mass index (BMI) was 28.2 ± 5.5 kg/m² in the old-cohort and 28.0 ± 5.7 kg/m² in the new-cohort. In the old-cohort 58.3% were men, in the new-cohort 53.5% were men. The mean change between the first and last % predicted FVC and FEV1 improved in both cohorts. The mean change of % predicted FVC and DLCO was significantly different between the two cohorts. Additional characteristics are shown in Table 3.

Patients treated with prednisone

In the old-cohort, 182 (49.3%) patients needed treatment with prednisone. In the new-cohort, 93 (43.7%) patients needed treatment with prednisone. The mean initial prednisone dose in the old-cohort was 32.1 ± 14.2 mg. Mean initial prednisone dose in the new-cohort was significantly lower, 21.4 ± 9.8 mg ($p < 0.001$). In the old-cohort, 62.6% of the patients started on ≤ 40 mg prednisone. In the new-cohort 57.0% of the patients started with prednisone according to the new protocol (i.e. on ≤ 20 mg prednisone). For some patients the explanation why their initial prednisone dose was higher than the protocol was provided by a pulmonologist (Table 4). Often the dose was higher when it concerned patients coming from a referral center. Before entering our cohort, the patients already started on a higher prednisone dose in another hospital. When arriving at our hospital, the 13 patients described in Table 4 were all put on prednisone tapering schemes and/or second-line therapy was introduced.

Pulmonary function

First mean % predicted FVC was 94.6 ± 19.8 in the old-cohort and 94.1 ± 22.0 in the new-cohort. First mean % predicted FEV1 was 84.8 ± 22.0 in the old-cohort and 84.5 ± 22.6 in the new-cohort. Mean % predicted DLCO was 73.2 ± 16.5 for the old-cohort and 74.8 ± 21.4 for the new-cohort (Table 5).

Average body mass index (BMI) was 27.6 ± 5.6 kg/m² in the old-cohort and 27.9 ± 6.0 kg/m² in the new-cohort. The mean change between the first and last % predicted FVC and FEV1 improved in both cohorts. The mean change of % predicted DLCO was significantly different between the two cohorts with 2.4 ± 9.3 increase and 1.3 ± 11.4 decrease in the old-cohort and new-cohort, respectively. This difference was not clinically relevant. Additional baseline characteristics are presented in Table 5.

BMI

First BMI measured for patients treated with prednisone in the old ($n=182$) and new ($n=97$) cohort did not differ between the cohorts, which was 27.6 ± 5.6 for the old and 27.9 ± 6.0 for the new-cohort. The second measured BMI was 27.5 ± 5.5 for the old and 28.1 ± 6.0 for the new-cohort. In Table 6, BMI measured at different time points is given for patients being treated with prednisone. BMI did not significantly differ at any point in time between the patients from the old and new-cohort.

Table 3. Characteristics of old-cohort versus new-cohort.

	Old-cohort n=369	New-cohort n=215	p-value [§]
Gender			
Male (n, %)	215 (58.3)	115 (53.5)	0.35
Female (n, %)	150 (40.7)	99 (46.0)	
Age (mean, ±SD)	49 ±12.2	51 ±13.0	0.09
BMI at first PFT (kg/m²)	28.2 ±5.5	28.0 ±5.7	0.47
Weight at first PFT	86.5 ±17.7	84.9 ±18.7	0.19
Treated with prednisone (n, %)	182 (49.3)	93 (43.7)	0.18
Mean first PFT (mean, ±SD)			
% predicted FVC	96.9 ±19.5	98.3 ±18.8	0.19
% predicted FEV1	88.5 ±21.1	89.0 ±20.4	0.64
% predicted DLCO	74.8 ±16.2	77.9 ±18.7	0.03
Mean change (mean, ±SD)[¶]			
% predicted FVC	1.9 ± 9.4	0.9 ±9.9	0.04
% predicted FEV1	0.9 ±9.3	0.3 ±10.1	0.60
% predicted DLCO	2.3 ±8.5	-0.5 ±9.7	0.00

§ p-values were calculated with a Mann-Whitney U test or Chi-square test.

¶ Number of months between 1st and last PFT was 23.1 ±13.4 (cohort 2015-2017) and 16.0 ±13.6 (cohort 2017-2019).

Abbreviations: DLCOc: diffusing capacity of lung for carbon monoxide (corrected for hemoglobin levels), PFT: pulmonary function, FVC: forced vital capacity, FEV1: forced expiratory volume in 1 second, kg: kilograms, mg: milligrams, m: meter.

Table 4. Overview of patients with higher initial prednisone dose.

Patient	Treated according to protocol	Short therapy overview by pulmonologist
1	Yes	Rightly treated according to protocol here. At first visit to our hospital prednisone already reduced by referral hospital to 10 mg (started elsewhere before referral to us at 60 mg). Steroid-saving MTX included.
2	Yes	On first visit 20 mg prednisone. Started with 60 mg elsewhere. Then reduced by 2.5 mg per month from 6-2018 to maintenance of 10 mg.
3	Yes	On first visit 20 mg prednisone. Elsewhere started with 60 mg. Started steroid-sparing after MTX evaluation. Reduction here also slightly slower (2.5 mg per 4 weeks instead of every 3 weeks).
4	Yes	Started with 60 mg prednisone due to renal sarcoidosis elsewhere in May 2018. Hereafter MTX was started and prednisolone was reduced.
5	No	Started with prednisone 60 mg elsewhere Sept 2017 due to cardiac sarcoidosis. Nov 2017 first seen here with still 60 mg prednisone. MTX (steroid-sparing) started immediately on our first visit, however this had to be discontinued due to hepatic MTX-toxicity. Therefore, prednisone was continued in quite a high dose with Azathioprine as a steroid-sparing therapy. So here due to circumstances and severity of cardiac sarcoidosis, a higher dose of prednisone was deliberately chosen for a longer period of time.
6	Yes	Started with 40 mg prednisone elsewhere. After referral to our hospital, MTX was started as steroid-sparing therapy and prednisone was tapered off (in 8 weeks to 10 mg).
7	Yes	Started with 40 mg prednisone elsewhere. After referral to our hospital steroid-sparing therapy with MTX and tapering of prednisone was started (adjusted tapering schedule, but in 3 months to 10 mg maintenance).
8	Yes	Came in with 10 mg of prednisone from elsewhere. MTX steroid-sparing therapy (BMI 28) and prednisone tapering was started in our hospital immediately.
9	Yes	Started prednisone elsewhere, starting dose unknown. When getting in, 15mg prednisone was taken. Elsewhere also started MTX from a steroid-saving point of view. At our center prednisone was directly further reduced to 10 mg maintenance
10	Yes	Came in with 20 mg of prednisone, which was started elsewhere. Starting dose elsewhere: 40 mg 2 days later immediately 20 mg. Immediately reduced here (per 2 weeks instead of per 3 weeks) due to BMI of 39. MTX built up immediately also from a steroid-sparing point of view.
11	Yes	Entering from elsewhere with 10 mg prednisone and 15mg MTX (from a steroid-sparing point of view). Prednisone immediately decreased to 0 mg (2.5 mg per 4 weeks) under plaquenil which was started with the purpose of also decreasing the MTX and providing plaquenil as monotherapy.
12	Yes	Came in with 10 mg prednisone. Elsewhere started with 40 mg. Started with steroid-sparing MTX at our center and prednisone was tapered (tapering schedule 2.5 mg every 4 weeks).
13	Yes	Came in with 5 mg prednisone from elsewhere and had methylprednisolone at our center in July 2018 due to severe cardiac sarcoidosis. Afterwards, MTX was started as steroid-sparing therapy due previous weight gain with prednisone.

Abbreviations: BMI: body mass index, MTX: methotrexate.

Table 5. Characteristics of patients on prednisone old-cohort versus the new-cohort.

	Old-cohort n=182	New-cohort n=93	p-value §
Gender			
Male (n, %)	109 (60.2)	50 (53.8)	0.46
Female (n, %)	72 (39.8)	43 (46.2)	
Age (mean, ±SD)	48 ±12.2	50 ± 12.8	0.18
Mean prednisone dose at start in mg (mean, sd)	32.1 ±14.2	21.4 ±9.8	0.00
BMI at first PFT (mean, ±SD)	27.6 ±5.6	27.9 ±6.0	0.86
Weight at first PFT (mean, ±SD)	84.8 ±17.5	84.5 ±18.7	0.74
Treated according to protocol (n, %)			
Yes, %	114 (62.6)	53 (57.0)	0.01
Mean initial prednisone dose (n, %)			
> 10 ≤ 20 mg	45 (24.7)	49 (52.7)	0.00
> 21 ≤ 30 mg	42 (23.1)	16 (17.2)	
> 31 ≤ 40 mg	27 (14.8)	6 (6.5)	
> 41 ≤ 50 mg	1 (0.5)	2 (2.2)	
> 51 ≤ 60 mg	15 (8.2)	1 (1.1)	
> 61 mg	2 (1.1)	0	
Initial dose missing, %	50 (27.5)	19 (20.4)	
Mean first PFT (mean, ±SD)			
% predicted FVC	94.6 ±19.8	94.1 ±22.0	0.95
% predicted FEV1	84.8 ± 22.0	84.5 ±22.6	0.87
% predicted DLCO	73.2 ±16.5	74.8 ±21.4	0.82
Mean change (mean, ±SD)[¶]			
% predicted FVC	2.6 ±10.2	2.0 ±9.4	0.25
% predicted FEV1	1.1 ±10.3	1.5 ±9.3	0.89
% predicted DLCO	2.4 ±9.3	-1.3 ±11.4	0.01

§ p-values were calculated with a Mann-Whitney U test or Chi-square test.

¶ Number of months between 1st and last PFT was 24.1 ±15.3 (cohort 2015-2017) and 12.3 ±11.4 (cohort 2017-2019).

Abbreviations: DLCOc: diffusing capacity of lung for carbon monoxide (corrected for hemoglobin levels), PFT: pulmonary function, FVC: forced vital capacity, FEV1: forced expiratory volume in 1 second, kg: kilograms, mg: milligrams, m: meter.

Table 6. BMI of patients treated with prednisone in the 2015-2017 versus the 2017-2019 cohort.

	Old-cohort	New-cohort	P-value
BMI at 1 st PFT (mean, \pm SD)	n=182 27.6 \pm 5.6	n=97 27.9 \pm 5.9	0.63
BMI at 2 nd PFT (mean, \pm SD)	n=182 27.5 \pm 5.5	n=97 28.1 \pm 6.0	0.40
BMI at 3 rd PFT (mean, \pm SD)	n=157 27.2 \pm 5.3	n=50 27.9 \pm 6.0	0.46
BMI at 4 th PFT (mean, \pm SD)	n=132 28.0 \pm 5.4	n=36 27.5 \pm 7.1	0.62
BMI at 5 th PFT (mean, \pm SD)	n=105 27.0 \pm 4.7	n=14 26.9 \pm 3.7	0.95

Continuous data are presented as mean \pm standard deviation.

Abbreviations: BMI: body mass index (kg/m²), PFT: pulmonary function test, kg: kilograms, m: meter. Time in months between the 1st, 2nd, 3rd, and 4th BMI measures were: 24.1 \pm 15.3, 26.5 \pm 14.8, 28.8 \pm 14.6, 31 \pm 15.2, respectively. For the new-cohort time in months was 12.3 \pm 11.4, 16.7 \pm 11.2, 19.3 \pm 12.0 and 29.3 \pm 14.2.

DISCUSSION

Statement of principal findings

In this study, we observed unchanged clinical outcome data after implementing a more conservative prednisone protocol in our sarcoidosis center. Specifically, the mean initial prednisone dose in the old-cohort was 32.1 \pm 14.2 mg and in the new-cohort 21.4 \pm 9.8 mg.

Comparing the old- and new-cohort, BMI did not significantly differ at any point in time, and change in % predicted FVC and FEV1 did not vary between the groups. These data suggest that a more conservative prednisone treatment has the potential to be equally effective in treating patients with pulmonary sarcoidosis. Change in % predicted DLCO was significantly different between the two groups. However, this difference was not clinically relevant.

The data of this study indicated that many referral patients from other clinics came in with a high dose of prednisone. Despite their high dose, these patients were treated following the new prednisone protocol in our center. Some did not meet the new start criteria (BMI > 25, DM, hypertension or osteoporosis) beforehand or met the new stop criteria. Often, prednisone was being phased out and/or a treatment indication for second-line treatment was started. This was the case in all 13 patients from whom therapy decisions were described in more detail. In addition, in one case due to circumstances and severity of (cardiac) sarcoidosis, pulmonologists needed to deviate from the protocol. Thus, for referral patients we have managed to lower the burden due to prednisone therapy.

Interpretation within the context of the wider literature

A retrospective study from The Netherlands consisting of 54 patients with pulmonary sarcoidosis concluded there was no clear association between prednisone dose and FVC change in newly-treated patients with pulmonary sarcoidosis.[15] Weight gain on the other hand was correlated with cumulative prednisone dose. Therefore, the authors concluded that prednisone treatment with a lower cumulative dose in the long term has the potential to be equally effective in treating patients with pulmonary sarcoidosis versus treatment with a higher dose strategy. Furthermore, lower dose prednisone treatment can reduce side-effects such as weight gain, mood swings and the development of diabetes. [14] Due to the adverse effects of prednisone and the lack of knowledge concerning the most optimal balance between dose and side-effects, lower (initial) dose and faster tapering seem to be equally effective.[14,15]

Although a more detailed analysis would be needed to conclude this, it seems that from what is known from the literature in combination with our analysis, the new protocol is equally effective.

As this improvement initiative was part of a value-based healthcare (VBHC) program, the new protocol was evaluated using data from daily clinical practice in combination with data from the literature. As reported elsewhere, despite the increasing interest in research on how to apply and translate knowledge into daily clinical practice and improve healthcare, the scientific knowledge in this field is slow.[21] Therefore rigorous evaluation of outcomes should remain part of research programs[21], also for future quality improvement initiatives for patients with pulmonary sarcoidosis.

Strengths and limitations

The structure of realizing the QI project was shaped making use of the PDSA cycle. This made it possible to have structure and support during the meetings and in the process of defining the QI initiative, which was also acknowledged by others.[22]

A limitation of this study is that we performed a before-after analysis. This study design does not control for bias that might have occurred at the same time.[23] Therefore, it remains difficult to determine whether the protocol change itself was responsible for the observed effect. Bias could have been that pulmonologists were already more conservative with prescribing prednisone before the new protocol was introduced based on insights from the literature. Also it would have been useful to study and evaluate the mean cumulative prednisone dosage over time and compare this to weight and BMI, which was done by other authors.[15] By doing this, it would be possible to draw conclusions that are more rigorous on the effect of the new dosage scheme. We were unable to collect detailed

information concerning the cumulative dosage retrospectively. It was hard to get detailed trustworthy data in retrospect.

Another limitation is that not all patients were treated according to the protocol. Just 53 patients (57.0%) were treated according to the protocol. Should this percentage have been higher, there could have been a stronger association between the mean BMI and respective difference between the old- and new-cohort. Also, before launching the new protocol, clinicians were already more careful with prednisone dosage, which can also partially explain there are no significant differences in BMI.

As presented in the results, in the old-cohort 62.6% and in the new-cohort 57.0% of the patients were treated according to the protocol. This clearly affected the results, as the other patients were treated with a different prednisone regimen. Due to circumstances and severity of extra-pulmonary sarcoidosis (such as cardiac sarcoidosis), a higher dose of prednisone was deliberately chosen for a longer period of time. Also, sometimes referral patients were on a high dosage of prednisone, but often our clinicians tried to taper down when possible. If more patients would have been treated according to the protocol, the results could have been stronger. However, the differences in mean initial dosage between the cohorts are quite significant (32 mg vs. 21 mg). Therefore, the results of this observational study are still meaningful.

Another limitation is that we did not provide regular (e.g. monthly) updates on how many patients started on prednisone and what their initial dosage was. This concerns step seven of the ICM model, providing continuous evaluation and feedback on the number of patients being treated with prednisone and their respective dosage scheme. It would have been useful to discuss the data of the number of patients starting on prednisone and their respective dosage after the implementation of the new protocol with the pulmonologists and the nurses from the ILD department.

Implications for policy, practice and research

As stated elsewhere, claims made from improvements are sometimes far stronger than is warranted.[23,24] We therefore suggest that our results can be used as a proof of concept, but we do suggest that the most optimal balance between prednisone dose, pulmonary function and side-effects should be studied in further detail. This can also be done as part of a prospective QI project, where the cumulative dosage of prednisone is also being monitored prospectively.

The continued work of measuring and comparing outcomes will allow discussing best practices and challenges in a multicenter setting. When there is constant monitoring

of health outcomes, this may have positive effects on outcomes. In a VBHC pilot study among IBD patients, positive trends such as fewer ED visits, fewer hospitalizations and less long-term corticosteroid use were observed.[25] When consistently monitoring outcomes in care delivered for patients with sarcoidosis, this can empower participating centers to implement and monitor QI efforts throughout the cycle of care.

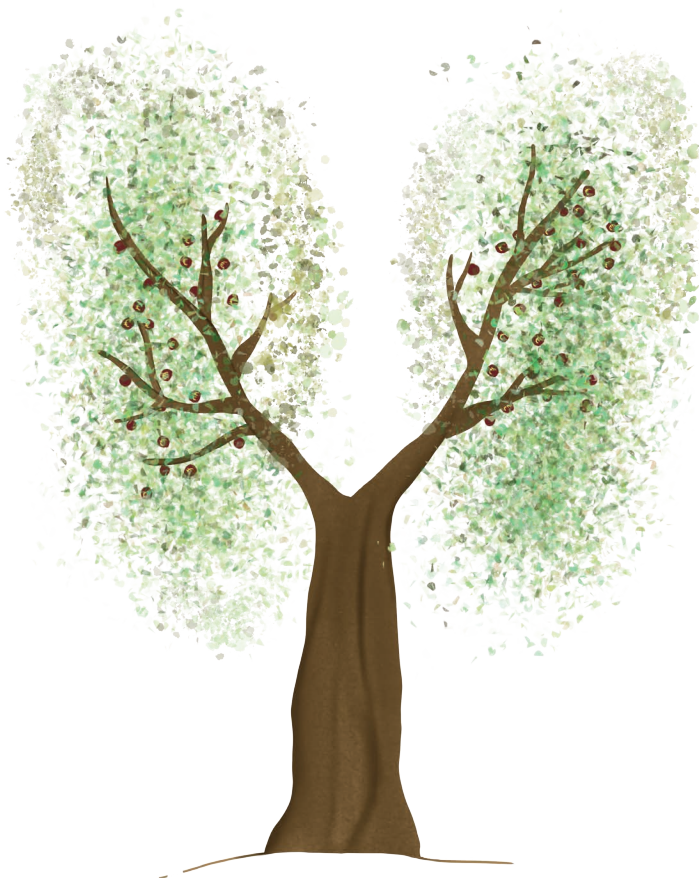
CONCLUSIONS

In summary, our study shows that VBHC principles can be applied in a sarcoidosis center. Furthermore, the collected outcome data support the observation that a more conservative prednisone regimen might be equally effective. Future research should however perform a more rigorous assessment of the clinical effectiveness of the different regimens on radiological improvement, extrathoracic disease improvement and quality of life.

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General Discussion and
Summary

Part
IV



General Discussion

7

GENERAL DISCUSSION

Increasing healthcare expenditures have triggered a trend using outcomes to improve quality and reduce costs. Value-based healthcare (VBHC) provides a framework and strategy shifting the focus from “volume” to “value”, where value is defined as the outcomes that matter most to patients divided by the healthcare delivery costs.[1] In order to improve value, one must first measure it.

This thesis investigated what measures should be part of a standard set of patient-relevant outcome measures for patients with pulmonary sarcoidosis, and how the standard set can be applied to improve value of care. Sarcoidosis is a relatively rare inflammatory multisystemic disease of unknown etiology, usually with a chronic course, for which currently no high quality evidence-based treatment and/or management recommendation are available. There is high unmet clinical need for healthcare improvement by other means. We have therefore implemented and evaluated the standard set in an international multicenter setting initiated by the St. Antonius Hospital. It was furthermore investigated if and how measurement of outcomes in the standard set can be used as a strategy to improve health outcomes. Finally, health care resource utilization and costs were presented.

This chapter discusses the main findings presented in this thesis and puts these results into a broader perspective. Reflections on the main findings are presented by discussing the following themes: conditions for using outcome measures, using outcome measures for quality improvement, applying VBHC in a rare chronic disease, the use of a global clinical registry system, and the evaluation of healthcare costs. Next, some methodological considerations are discussed. Finally, implications and recommendations are provided for clinical practice, policy and research.

REFLECTION ON THE FINDINGS

CONDITIONS FOR USING OUTCOME MEASURES

Using outcome measures for quality improvement

In our review (Chapter 2) we showed that successful quality improvement (QI) and consequently improved outcomes, is dependent on an active approach and organizational readiness. There are various QI methods, and the majority of improvement interventions contain a combination of several methods. Clinical registries can be seen

as supportive instruments in the process of improving the quality of care.[2] However, a clinical registry can only be successful in realizing QI efforts when there is commitment and leadership at both the physician and manager level, as well as a benchmarking facility, a well-integrated computerized system, and a collective aim to identify best practices. In line with our review, Litton et al. (2020) presented various lessons learned from quality improvement initiatives using clinical registries targeting patients admitted to the intensive care unit. It was concluded that having clinical registries were highly effective tools for identifying and reducing unwarranted practice variation.[2] They furthermore concluded that dealing with real time data requires planning, infrastructure and resourcing.

In our project, we tried to incorporate the lessons learned from our review. First, we developed a well-integrated web-based platform, for which we made use of REDCap. This is widely used metadata-driven software and contains workflow methodology for designing clinical and translational databases. The data collected by the six participating centers formed the basis for scientific analysis and discussions we have had concerning the quality of care and clinical practice variations. Second, there was very strong commitment from the participating clinicians. We experienced that when there were research nurses or other research staff involved, there was strong(er) ownership of the project. Finally, there was a collective aim to find best practices and exchange ideas on how to improve care for patients with pulmonary sarcoidosis.

Value based healthcare in a rare chronic disease

The treatment of sarcoidosis shows significant variation in clinical practice. There is a lack of clear and robust evidence-based recommendations for diagnostic and management pathways. Therefore, in Chapter 3 we developed a consensus-driven patient-centered standard set, enabling international comparison of clinical outcomes for patients with pulmonary sarcoidosis. Multicenter data collection might allow researchers to review these variations in clinical practice across different hospitals and learn from it by comparison (Chapter 4). Furthermore, insights gained from registries have the potential to provide support to clinicians composing clinical guidelines. In addition, measuring results will allow teams to know if they are succeeding.[3] Measuring health outcomes furthermore provides the data needed to improve care. With these goals in mind, more standard sets have been developed in various patient groups.[4–8]

Especially in orphan and chronic diseases, VBHC can be of great value, as there is little data coming from randomized clinical trials and longitudinal data collections are scarce. [9] Furthermore, outcomes of treatment and care delivery are diverse and difficult to quantify.[9] Additionally, care delivery for the treatment of patients with pulmonary sarcoidosis is not so much protocolled and standardized/evidence based. Therefore,

applying VBHC in a chronic and/or orphan disease can be seen as an opportunity. A strength of applying VBHC is that one gets insights into clinical outcomes faster compared to e.g. a randomized clinical trial. Thereby, insights resulting from VBHC might be useful for improvement of care for rare diseases. Our aim was to find scientific support for this.

We have provided this in Chapter 6, where we introduced a more conservative prednisone protocol. The protocol for prednisone treatment was selected as an intervention after seven team meetings with a quality improvement team, where various outcomes and quality of care topics were being discussed. In the new protocol, prednisone intake was reduced from a starting dose of 40 mg to a starting dose of 20 mg. The new protocol showed to be equally effective looking at the changes in pulmonary function and BMI. We therefore gained important insights related to the pharmacological management pathway for patients with pulmonary sarcoidosis. To conclude, we have shown that applying VBHC principles in a sarcoidosis center of expertise can promote the delivery of high-value clinical care.

Global clinical registry system

In a review paper on pulmonary sarcoidosis it was addressed there is a need for more randomized, controlled, multicenter and international clinical trials.[10] However, there are many obstacles including financial ones, that hinders its development, especially with regard to recent treatment recommendations of ERS.[11] A registry system might be useful to improve clinical outcomes and pharmacological management of patients with (pulmonary) sarcoidosis in real world settings. Especially in an orphan disease, international collaboration is key to collect sufficient data for robust analysis providing insights into the most optimal treatment.

An example of a national registry is the British Thoracic Society Sarcoidosis Registry which aims to phenotype sarcoidosis in the UK.[12] In addition to this goal, it would be useful to use global registries as a basis to gain and exchange insights at an international level in order to realize improvements in e.g. patients' drug regimes. Indeed, there is a need to further optimize the use of pharmacotherapeutic interventions in order to individualize treatment while improving or (at least) maintaining the quality of life for patients with sarcoidosis.[13]

In our study we have followed up patients for a relative short term (Chapter 4). A more advanced registry system aiming to collect longitudinal data will allow to evaluate the clinical outcomes (such as quality of life, pulmonary function, blood biomarkers and the incidence of side effects). This would enable caregivers to make use of insights derived from clinical outcomes measured over a longer period. Such data resulting from registries

can be of great importance to determine e.g. the pharmacological management pathway for patients with sarcoidosis.[12]

We experienced that having a clinical registry system in place for patients with pulmonary sarcoidosis can be very useful. As pointed out earlier, we made use of REDCap, allowing multicenter access. We have had good experiences using REDCap. Other clinical data management systems (CDMS) can be more expensive for investigator-initiated studies or other studies at a smaller scale. REDCap is however not expensive and attempts to facilitate informatics support for clinical researchers and foster a collaborative network. The only limitation was that we were unable to link the electronic patient record to REDCap, which could potentially lower the burden caused by manual data entry. Furthermore, we would advise to have a research nurse or researcher in place at every center, facilitating and guiding the data collection process.

For project-based research projects, REDCap can be very helpful. However, for quality registries to support quality improvement in routine clinical care other CDMS might be more suitable.

Organizational readiness & safety culture

Throughout our project, we experienced a very open and safe culture among the participating clinicians. However, we did not measure this. Safety culture is defined as "the product of individual and group values, attitudes, perceptions, competencies, and patterns of behavior that determine the commitment to, and the style and proficiency of, an organization's health and safety management".[14] There is evidence that culture influences both patient and staff related outcomes.[2] In other work it was highlighted that it is important to have good team cohesion, open communication, and proper problem solving conflict management.[15] Moreover, a positive interaction between doctors, nurses and other staff is associated with lower risk-adjusted length of stay, better quality of care and a lower nurse turnover.[16, 17] Conversely, factors such as fear, lack of mutual respect and top-down/dictatorial leadership behavior may adversely affect the (safety) culture and negatively affect outcomes.[18] Therefore, when discussing outcomes during sessions with multiple hospitals for example, building trust and creating a safe culture are key. When comparing results, there should be a focus and culture to learn from each other.

METHODOLOGICAL CONSIDERATIONS

Several methodological considerations should be taken into account when interpreting results as presented in this manuscript. Most of them have been discussed in the respective chapters. Four topics will be discussed below.

Evaluating Costs

As part of the VBHC principles, time-driven activity-based costing (TDABC) has been suggested as the method capable of addressing costing issues.[19] TDABC was presented by Kaplan and Anderson as a solution to healthcare's cost-crisis. The method requires two key parameters: the capacity cost rate (CCR) as well as the time spent to perform service delivery activities. A recent review on TDABC concluded this costing method helps to address the challenge of costing in healthcare.[20] TDABC's ability to inform bundled payment reimbursement systems remains however to be demonstrated in the scientific literature. Thus, it is not yet proven TDABC is the universal method identifying costs. In our project, we have not applied TDABC as we found less time-consuming methods helping to answer our research questions.

In Chapter 5 we have used a different model to analyze costs, where we looked into the most expensive patients. This method is less complicated and takes less time compared to the TDABC method. Especially for patients with a chronic disease course, it can be of interest to measure total costs over a full treatment period per patient and to identify the most expensive treatment period looking at the patient cohort. In addition, it might be interesting to include the societal costs. This includes costs due to work loss of patients not being able to work due to the severity of their disease course, which can be very relevant for patients with pulmonary sarcoidosis. Multiple methods may be relevant depending on the goal and setting.

For hospitals with centers of expertise for rare/complex disorders (such as pulmonary sarcoidosis), it is important to have an understanding of all related healthcare costs in order to e.g. negotiate better reimbursement and/or compensation fees. In a center of expertise such as the St. Antonius hospital the case mix becomes more complex, resulting in disproportionate costs. In a funding system based on benchmarking, it is more difficult for hospitals with such centers of expertise, especially for the non-academic ones. They cannot easily claim compensation appointed by the government. Information regarding costs and cost drivers can support in the discussion and lobby for compensation.

We analyzed the costs for patients with sarcoidosis treated at the St. Antonius Hospital in the Netherlands. We did not use cost data from other centers. As a consequence, we

were unable to perform a multi-center study focused on costs. Also, we were unable to include the societal costs, such as costs due to productivity loss of patients (or sometimes other family members as well), not being able to work due to the severity of their disease. For patients, addressing and measuring this can be of great importance and a valuable addition. Questionnaires could be used asking patients whether the disease impacted work, how this impacted their financial situation and how this consequently impacted their quality of life.

Data quality

Ideally, in order to have the best data quality, there should be a direct link with the electronic patient record. When there is a semi-automated system in place, this has the potential to reduce the registration burden for healthcare professionals, and increase the willingness to participate in future registry-related initiatives. Most of the data collected in the participating centers were entered manually into REDCap, as an automated system for extracting these data in the respective centers does not currently exist.

Data presented in Chapter 3 and Chapter 4 were collected retrospectively. Patients visited the clinic at different points in time, which made it more difficult to evaluate and compare data. Furthermore, the six centers that collected data measured and reported some outcomes differently due to international variation, such as ethnicity. In some centers ethnicity is not registered and can therefore only be evaluated based on photographs in the electronic patient record. There might however be more differences in registration between hospitals that are not easily identified as being inadequate.

Variation in healthcare systems

Underlying variation in routine daily clinical practice may exist due to differences in care pathways, but are also due to reimbursement differences between countries. This may impact variation in clinical outcomes, which are difficult to measure and quantify. In the USA it is for example expensive to perform a PET scan (and this is not always reimbursed), resulting in lower numbers of PET scans compared to the Netherlands. Performing a PET scan in sarcoidosis patients provides information on the underlying metabolic changes, which is useful to determine the extent and inflammatory activity of the disease.[21] In our project, although difficult to quantify, we had multiple discussions regarding the differences in diagnostics and treatment and when this could potentially impact outcomes.

IMPLICATIONS FOR CLINICAL PRACTICE, POLICY & RESEARCH

We have drafted the following recommendations for clinical practice, policy & research. Some recommendations build on ongoing initiatives that can be further extended. All recommendations need further validation in an experimental and/or scientific context.

Implications for clinical practice

It all starts with having a dedicated multidisciplinary team where people trust each other, and where results on performance can be openly discussed. As also acknowledged in our review, there should be commitment and leadership, also among clinicians. The (open) culture and willingness to change is important, also in a setting where (inter)national collaborations are in place, and when practice variations are being discussed.

Based on our experiences with the VBHC projects in this thesis we have formulated the following recommendations aimed at setting up a project group to implement VBHC practices and to optimize patient care:

- Make patients part of working groups when defining standard sets.
- Have a data collection tool in place enabling (international) data collection.[22] This is absolute key in order to have a common ground. In addition, all stakeholders should trust the data presented.
- Have a dedicated person in each center to manage the data collection process.
- Publish outcome measures in the public domain. This may promote realizing improvements in care, as centers are more likely to discuss results and (ex)change (best) practices. Transparency can make physicians and nurses aware of practice variations and may help to improve care.
- Routinely measure QoL in daily clinical practice can be an outcome measure of great importance. It would be of great value if future registries for patients with pulmonary sarcoidosis include QoL measures. Specifically, incorporating QoL enables to evaluate if value had gained from the perspective of the patient. Although some centers measure this, QoL is rarely being followed-up on a systematic basis and linked to important clinical outcomes such as linking QoL to pulmonary function variables.
- Measure costs and link them to clinical outcomes. Efforts to further improve the quality of care and clinical outcomes for patients with sarcoidosis could specifically target patients with many comorbidities, which are often the most expensive patients. Although this is not the aim of measuring costs and linking them to outcomes, by doing this, this can potentially reduce the overall costs.
- Financial support from the management and the board of directors for data collection.

- Use cost data for novel strategies/methods for compensation of expert centers for rare and/or complex disorders to ensure durability of these centers and continuity of optimal healthcare for these diseases in the future.

Implications for Policy

An objective of the Ministry of Health, Welfare and Sport is to have outcome information available for 50% of the disease burden by 2022. This can further promote shared decision-making. The Dutch Ministry of Health, Welfare and Sport stimulates further development of VBHC. One of the initiatives supporting this is the program “*Uitkomstgerichte zorg*” (2018-2022) of which the goals are two-fold: 1) to improve the quality of life for the patient and 2) to increase job satisfaction for quality delivery.[23] This thesis yielded the following recommendations for policy:

- Future (inter)national policy efforts should focus on the development and use of standard sets, measuring and assessing the quality of care across different centers and countries. Indeed, this should facilitate informative comparisons of practice variations between various centers and countries.
- Future policy efforts should continue to address the importance of focusing on “value” and not on “volume”.

Implications for Research

This dissertation leads to an agenda for future research in several ways. First, our standard set was not validated with patients. Recently, the manuscript titled “SCOUT – Sarcoidosis Outcomes Taskforce. A systematic review of outcomes to inform the development of a core outcome set for pulmonary sarcoidosis” was published.[24] This study identified outcomes reported in registered clinical trials and in literature, exploring the experiences of patients with pulmonary sarcoidosis. Together with patient representatives, our standard set for pulmonary sarcoidosis should be evaluated and updated. Consensus should be reached with patients, healthcare professionals, researchers in the field and industry representatives.

Second, besides the standard set, other outcomes should be measured for patients with pulmonary sarcoidosis. In order to interpret and improve outcomes, gaining insights into the process is needed. As we have discussed earlier, medication and changes in medication use (both dosage and changes in first/second/third line medication) should be tracked systematically. This could be linked to the patients' QoL. Ideally, this data is then stored in the electronic patient record and will become available to physicians and patients, which can then be discussed together. It would be of value to evaluate the current medication management and relate this to the patients' QoL systematically, as

this largely impacts the patients' quality of life. This has the potential to better substantiate changes in the disease management of patients with pulmonary sarcoidosis.

Third, in order to have data suitable for (inter)national comparison, reliable data and IT systems are key. Having reliable data and IT systems can be used to identify target groups, to align healthcare providers and provide consistent reference data as well as to inform healthcare providers with real-time treatment and outcome data. Ideally, they are linked to electronic patient records. In many hospitals current data entry tools and reporting requirements are inefficient and often frustrating. When there are attractive (e.g. automated) data entry tools in place, this will decrease the burden caused by manual data entry and stimulate the (inter)national willingness to participate in these kind of networks. Therefore, efficient IT systems should be developed. Healthcare workers should participate in the design of IT systems collecting outcome data.

Fourth, within other interstitial lung diseases (ILDs) applying VBHC principles has the potential to improve care delivery. A chronic, progressive and ultimately fatal disease such as idiopathic pulmonary fibrosis (IPF) can benefit from applying VBHC. The management of IPF is complex due to disease progression and its unpredictability.[25] Furthermore, the treatment of IPF is complex due to the significant symptom burden and the changing care and education needs of patients throughout the course of the disease. When there is access to high-quality (inter)national data on outcomes of patients with IPF, clinicians can integrate this in disease management. In addition, other chronic diseases can benefit from applying VBHC principles. Therefore, future research should investigate whether applying VBHC for e.g. patients with IPF can be of value.

Fifth, how to measure costs within VBHC remains unclear. Future research efforts should further evaluate, depending on goals and setting, whether time-driven activity based costing (TDABC) is indeed the preferred activity-based costing method within VBHC. Also acknowledged elsewhere, in order to further elaborate on the value for patients alongside the VBHC framework, it is needed to also evaluate costs of treatments systematically.[26] Moreover, value can not only be increased by improving outcomes, but also by lowering costs. Assessing costs thoroughly is necessary in order to define value for the patient. In addition, it will enable a center of expertise to gain information regarding costs and cost drivers which can help in the discussion and negotiations *for* reimbursement and/or other compensations.

GENERAL CONCLUSIONS

This thesis provides evidence that VBHC principles can be applied in hospitals treating patients with pulmonary sarcoidosis. We have developed a standard set of outcome measures that can be used to compare clinical outcomes of different sarcoidosis centers. The standard set can support further implementation of VBHC and standardization of collecting outcomes for patients with pulmonary sarcoidosis. Efforts on systematically measuring outcomes create opportunities for improving treatment decision making and realizing benchmarking across sites, both on a regional and international level.

Finally, the collected outcome data supported the observation that a more conservative prednisone regimen might be equally effective in treating the inflammation while maintaining quality of life and reducing side-effects. By applying VBHC, we have derived quick and novel insights for patients with pulmonary sarcoidosis.

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Summary

8

SUMMARY

This thesis focuses on the development, implementation and evaluation of a patient-relevant standard set of outcome measures for patients with pulmonary sarcoidosis. The aim of this thesis was to investigate whether value-based healthcare (VBHC) can be of use for improving the care for patients with pulmonary sarcoidosis. We formulated the following research questions:

1. What outcomes and measures should be part of a patient-centered standard set of outcome measures for patients with pulmonary sarcoidosis in a multicenter setting?
2. How can outcome measures from clinical registries help to implement and monitor quality improvement initiatives? What are facilitators and/or barriers that contribute to the realization of QI efforts?
3. What is the feasibility to use the set of outcome measures for patients with pulmonary sarcoidosis in a multicenter setting?
4. When applying VBHC-principles, what is a best practice for patients with pulmonary sarcoidosis and how did this best practice affect outcomes?
5. What are utilization patterns and healthcare costs in patients with sarcoidosis?

Part I. Health outcome measurement and quality improvement

Clinical registries function as an important tool to systematically measure and evaluate clinical outcomes. In **Chapter 2**, we conducted a systematic review summarizing the results of studies that use outcome measures from clinical registries to implement and monitor quality improvement (QI) initiatives. There are many different QI methods. The majority of improvement interventions identified in the systematic review are a combination of several methods. We concluded that clinical registries are supportive instruments in the process of continuously improving the quality of care. However, a clinical registry can only be successful in realizing QI efforts when there is commitment and leadership at both the physician and manager level. In addition, there should be a benchmarking facility, a well-integrated computerized system, and a collective (institutional) aim to identify best practices in place.

Part II. Development and evaluation of the standard set of outcome measures for pulmonary sarcoidosis

For patients with pulmonary sarcoidosis no standard sets of outcome measures had been developed yet. Therefore, in **Chapter 3** we developed a consensus-driven, patient-centered standard set, enabling international comparison of clinical outcomes for patients with pulmonary sarcoidosis. This standard set of outcome measures was developed in collaboration with five sarcoidosis expert clinics. Seven outcomes and associated measures

were identified: mortality (1 and 5 years), pulmonary function (FEV1, FVC, DLCOc), sIL-2R change as an activity biomarker, weight gain, quality of life (measured with the King's Sarcoidosis Questionnaire and the Fatigue Assessment Scale), osteoporosis, and clinical outcome status (COS). Routine data collection based on standardized outcome measures creates an opportunity to improve patient care. A reliable data collection process for patients with pulmonary sarcoidosis enables clinicians to compare outcomes between various clinics/treatments, which can ultimately help to identify best practices. Applying this outcome set has the potential to better inform patients, healthcare providers and other stakeholders in stimulating value-based healthcare for patients with pulmonary sarcoidosis.

Next, in **Chapter 4**, we present the evaluation of the standard set of outcome measures. We showed that collecting data in a retrospective multicenter international cohort is feasible for the outcomes mortality, pulmonary function, weight changes and COS. Conversely, it was not (yet) feasible to collect data for international comparisons on QoL, sIL-2R and osteoporosis.

We have developed a standard set of outcome measures that can be used both retrospectively and prospectively to compare clinical outcomes of different sarcoidosis centers. This set supports further standardization of collecting outcomes for pulmonary sarcoidosis patients globally aiming to improve treatment decision making. Besides, benchmarking between different healthcare systems can be realized, both on a regional and international level.

Part III. Implementation of best practice & costs

In **Chapter 5**, we identified cost-related information and described characteristics of 200 patients with sarcoidosis in a Dutch patient cohort using administrative data. The mean overall healthcare costs of the top 1% patients with sarcoidosis were 22 times higher compared to that of the random sample of the bottom 95% (€108.296 vs. €4.817, respectively). The mean annual healthcare costs of the top 1% patients with sarcoidosis were six times higher compared to that of the random sample of the bottom 95% (€51.082 vs. €8.692, respectively). Treatment time of the most expensive 1% was 2.5 times longer compared to the random sample. The top 1% patients and top ≥1-5% patients showed to have more sarcoidosis related organ involvement compared to the random sample of the bottom 95%, indicating that those are patients with more advanced sarcoidosis. Unexpectedly, patients with and without fatigue showed to have comparable mean overall costs and annual costs. The top three cost-drivers identified in both the top 1% and top ≥1-5% high-cost patients were: 1) expensive medication, 2) intensive care/general ward nursing, and 3) costs made at the Respiratory Medicine department. Efforts to further

improve the quality of care and clinical outcomes for patients with sarcoidosis could specifically target the most expensive patients, which can potentially reduce the overall costs.

In **Chapter 6**, we identified an improvement intervention that was selected after evaluating the standard set of outcome measures presented in Chapter 4. We found that patients with long-term prednisone use had a higher BMI and that their BMI increased more compared to patients using prednisone for a shorter time, which was also known from the literature. Therefore, we developed, implemented and evaluated a new prednisone protocol for patients with sarcoidosis. The new protocol was evaluated using data from daily clinical practice. This was studied in a single center observational study. The new prednisone protocol included a conservative regimen and was reduced to receiving 20 mg at start as the golden standard in the clinic from the 1st of September 2017 onwards.

The new protocol did not cause major clinical changes in pulmonary function nor in BMI. No major clinical differences were observed in the mean change in the FVC% predicted, FEV1% predicted and DLCO % predicted. Therefore, the collected outcome data support the observation that a more conservative prednisone regimen might be equally effective. The continued work of measuring and comparing outcomes will allow discussing best practices and challenges in a multicenter setting. Constant monitoring of health outcomes may have positive effects on outcomes.

CONCLUSIONS

In conclusion, this thesis has provided evidence that VBHC principles can be applied in hospitals treating patients with pulmonary sarcoidosis. We have developed a standard set of outcome measures that can be used to compare clinical outcomes of different sarcoidosis centers. The set can support further implementation of VBHC and standardization of collecting outcomes for patients with pulmonary sarcoidosis. Finally, the collected outcome data support the observation that a more conservative prednisone regimen might be equally effective in treating the inflammation while maintain quality of life and reducing side-effects. By applying VBHC, we have derived fast and novel insights for patients with pulmonary sarcoidosis.

This standard set of outcome measures has the potential to improve treatment decision making. Furthermore, benchmarking across sites can be realized, both on a regional, national and international level.



Appendices

Nederlandse Samenvatting

Affiliations of the Authors

List of Publications

Curriculum Vitae

PhD Portfolio

Dankwoord

NEDERLANDSE SAMENVATTING

Dit proefschrift richt zich op de ontwikkeling, implementatie en evaluatie van een standaardset van uitkomstindicatoren voor patiënten met pulmonale sarcoïdose. Het doel van dit proefschrift was om te onderzoeken of waardegedreven zorg, oftewel value-based healthcare (VBHC), van toegevoegde waarde kan zijn bij het ontwikkelen van zorg voor patiënten met pulmonale sarcoïdose. We hebben de volgende onderzoeksvragen geformuleerd:

1. Welke uitkomsten en indicatoren moeten deel uitmaken van een standaardset van uitkomstindicatoren voor patiënten met pulmonale sarcoïdose in een multicenter setting?
2. Hoe kunnen uitkomsten uit kwaliteitsregistraties helpen bij het implementeren en monitoren van kwaliteitsverbeteringen? Wat zijn katalysatoren en barrières die bijdragen aan het realiseren van kwaliteitsverbeteringen?
3. Hoe haalbaar is het om de standaardset van uitkomstindicatoren voor patiënten met pulmonale sarcoïdose te meten in een multicenter setting?
4. In het toepassen van VBHC, wat is een 'best practice' voor patiënten met pulmonale sarcoïdose en hoe beïnvloedt deze 'best practice' uitkomstindicatoren voor patiënten met pulmonale sarcoïdose?
5. Hoe ziet het zorggebruiker eruit en wat zijn de zorgkosten van patiënten met sarcoïdose?

Deel I. Evalueren van uitkomstindicatoren en kwaliteitsverbetering

Een kwaliteitsregistratie is een belangrijk instrument om klinische uitkomsten systematisch te meten en te evalueren. In **Hoofdstuk 2** presenteerden we een overzicht van onderzoeken die uitkomstindicatoren uit kwaliteitsregistraties gebruiken om verbeterinitiatieven te implementeren en monitoren. Er zijn veel verschillende methoden om kwaliteitsverbeteringen te realiseren. De meeste verbeterinitiatieven die in de systematische review zijn geïdentificeerd, zijn een combinatie van verschillende methoden. We concludeerden dat kwaliteitsregistraties ondersteunende instrumenten zijn in het proces van het continu verbeteren van de kwaliteit van zorg. Een kwaliteitsregistratie kan echter alleen succesvol zijn in het realiseren van verbeterinitiatieven als er commitment en leiderschap is van zowel de zorgverlener als manager. Daarnaast moet er een benchmarkingfaciliteit zijn, een goed geïntegreerd geautomatiseerd systeem en een collectief (institutioneel) doel om bestaande 'best practices' te identificeren.

Deel II. Ontwikkelen en evalueren van een standaardset van uitkomstindicatoren voor pulmonale sarcoïdose

Voor patiënten met pulmonale sarcoïdose was nog geen standaardset van uitkomstindicatoren ontwikkeld. Daarom hebben we in **Hoofdstuk 3** een consensusgedreven, patiëntgerichte standaardset van uitkomstindicatoren ontwikkeld die internationale vergelijking van klinische uitkomsten voor patiënten met pulmonale sarcoïdose mogelijk maakt. Deze standaardset van uitkomstindicatoren is ontwikkeld in samenwerking met vijf sarcoïdose expertise centra. Er werden zeven uitkomsten en daaraan gekoppelde uitkomstindicatoren geïdentificeerd: mortaliteit (1-jaarsoverleving en 5-jaarsoverleving), longfunctie (FEV1, FVC, DLCOc), sIL-2R-verandering als marker voor pulmonale ziekteactiviteit, gewichtsveranderingen, kwaliteit van leven (gemeten met de 'King's Sarcoidosis Questionnaire' en de 'Fatigue Assessment Scale'), osteoporose en 'clinical outcome status' (COS). Het routinematig verzamelen van gegevens op basis van gestandaardiseerde uitkomstindicatoren biedt handvatten om de patiëntenzorg te verbeteren. Een betrouwbaar proces voor het verzamelen van gegevens voor patiënten met pulmonale sarcoïdose stelt zorgverleners in staat de resultaten tussen verschillende centra én behandelingen te vergelijken, wat uiteindelijk kan helpen bij het identificeren van 'best practices'. Het toepassen van deze standaardset van uitkomstindicatoren heeft het potentieel om patiënten, zorgverleners en andere belanghebbenden beter te informeren over het bevorderen van waardegedreven zorg voor patiënten met pulmonale sarcoïdose.

Vervolgens hebben we in **Hoofdstuk 4** de resultaten gepresenteerd van de evaluatie van de standaardset van uitkomstindicatoren. We toonden aan dat het verzamelen van data in een retrospectief multicenter internationaal cohort haalbaar is voor de uitkomsten mortaliteit, longfunctie, gewichtsveranderingen en COS. Het was echter (nog) niet haalbaar om data te verzamelen voor kwaliteit van leven, sIL-2R en osteoporose.

We hebben een standaardset van uitkomstindicatoren ontwikkeld die zowel retrospectief als prospectief kan worden gebruikt om klinische uitkomsten van verschillende sarcoïdosecentra te vergelijken. Deze set ondersteunt verdere standaardisatie van het verzamelen van resultaten voor patiënten met pulmonale sarcoïdose wereldwijd met als doel de besluitvorming rondom de behandeling te verbeteren. Daarnaast kan benchmarking tussen verschillende zorgsystemen worden gerealiseerd, zowel op regionaal, nationaal als internationaal niveau.

Deel III. Implementatie van 'best practice' & kosten

In **Hoofdstuk 5** hebben we het zorggebruik en zorgkosten geïdentificeerd en kenmerken beschreven van 200 patiënten met sarcoïdose in een Nederlands patiëntencohort. De

gemiddelde totale zorgkosten van de top 1% van de patiënten met sarcoïdose waren 22 keer hoger dan die van de steekproef van de onderste 95% (€108,296 versus €4,817, respectievelijk). De gemiddelde jaarlijkse zorgkosten van de top 1% waren zes keer hoger dan die van de steekproef van de onderste 95% (€51,082 versus €8,692, respectievelijk). De behandeltime van de duurste 1% was 2,5 keer langer in vergelijking met de patiënten afkomstig uit de steekproefselectie. De top 1% patiënten en top ≥1-5% patiënten toonden meer sarcoïdose-gerelateerde orgaanbetrokkenheid in vergelijking met de steekproef van de onderste 95%, wat aangeeft dat dit vaker patiënten zijn met gevorderde sarcoïdose. Tegen onze verwachting in bleken patiënten met en zonder vermoedingsklachten vergelijkbare gemiddelde totale zorgkosten en jaarlijkse zorgkosten te hebben. De drie belangrijkste kostendrijvers die werden geïdentificeerd in zowel de top 1% als de top ≥1-5% duurste patiënten waren: 1) dure medicatie, 2) intensive care/algemene verpleegafdeling, en 3) kosten gemaakt op de afdeling Longgeneeskunde.

Inspanningen om de kwaliteit van zorg en klinische resultaten voor patiënten met sarcoïdose verder te verbeteren, zouden specifiek gericht kunnen worden op de duurste patiënten, wat mogelijk de totale kosten kan verlagen.

Op basis van de evaluatie van de standaardset identificeerden we een verbeterinitiatief. Dit is beschreven in **Hoofdstuk 6**. We ontdekten dat patiënten met langdurig prednisongebruik een hogere BMI hadden en dat hun BMI meer toenam in vergelijking met patiënten die prednison voor een kortere tijd gebruikten. Dit is ook bekend vanuit de literatuur. Daarom hebben we een nieuw conservatief prednisonprotocol voor patiënten met sarcoïdose ontwikkeld, geïmplementeerd en geëvalueerd.

Het nieuwe protocol is geëvalueerd aan de hand van gegevens uit de dagelijkse klinische praktijk. Dit werd onderzocht in een observationeel onderzoek in één centrum. Het nieuwe prednisonprotocol was gebaseerd op conservatieve toepassing en werd bij aanvang teruggebracht tot 20 mg en per 1 september 2017 als gouden standaard gehanteerd.

Het nieuwe protocol veroorzaakte geen grote klinische veranderingen in de longfunctie, noch in de BMI. Er werden geen grote klinische verschillen waargenomen in de gemiddelde verandering van de FVC%, FEV1% en DLCO% voorspelde waarden. Daarom ondersteunen de verzamelde uitkomstgegevens de observatie dat een conservatiever prednison beleid even effectief zou kunnen zijn.

Het voortdurende werk van het meten en vergelijken van behandelresultaten zal het mogelijk maken om 'best practices' en uitdagingen te bespreken in een multicenter

setting. Wanneer de gezondheidsuitkomsten constant worden gemonitord, kan dit een positief effecten hebben op de uitkomsten.

CONCLUSIES

Concluderend levert dit proefschrift bewijs dat VBHC-principes succesvol kunnen worden toegepast in ziekenhuizen die patiënten met pulmonale sarcoïdose behandelen. We hebben een standaardset van uitkomstindicatoren ontwikkeld waarmee klinische uitkomsten van verschillende sarcoïdose centra kunnen worden vergeleken. De set kan de verdere implementatie van VBHC en standaardisatie van het verzamelen van resultaten voor patiënten met pulmonale sarcoïdose ondersteunen. Ten slotte ondersteunen de verzamelde uitkomstgegevens de observatie dat een conservatiever prednisonregime even effectief zou kunnen zijn. Door VBHC toe te passen, hebben we aangetoond dat we tot snelle en nieuwe inzichten komen waardoor de meest optimale behandelstrategie wordt terugvertaald naar de klinische praktijk.

De standaardset van uitkomstindicatoren heeft de potentie om de besluitvorming rondom de behandelstrategie te verbeteren. Tevens kan dit benchmarking faciliteren tussen ziekenhuizen, zowel op regionaal, nationaal als internationaal niveau.

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LIST OF PUBLICATIONS

Harman NL, Gorst SL, Williamson PR, Barnathan ES, Baughman RP, Judson MA, Junk H, **Kampstra NA**, Sullivan EJ, Victorson DE, Walton M, Al-Hakim T, Nabulsi H, Singh N, Grutters JC, Culver DA. Scout - sarcoidosis outcomes taskforce. A systematic review of outcomes to inform the development of a core outcome set for pulmonary sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis.* 2021;38(3):e2021034.

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Kampstra NA, Van Hoan N, Koenders DJPC, Schoop R, Broersen BC, Mouquet-Rivier C, Traoré T, Bruins MJ, de Pee S. Energy and nutrient intake increased by 47-67% when amylase was added to fortified blended foods-a study among 12- to 35-month-old Burkinabe children. *Matern Child Nutr.* 2018 Jan;14(1):e12459.

CURRICULUM VITAE



Nynke Kampstra was born on February 26, 1988 in Leeuwarden, the Netherlands. After finishing secondary school at the Dockinga College in Dokkum, she studied Nutrition & Dietetics at the Hanze University of Applied Sciences in Groningen. She continued her academic education with the master's program Public Health & Society at the Wageningen University. During her studies she worked at the World Health Organization (WHO) headquarters for her thesis project. For her internship and consultancy period, Nynke worked with the World Food Programme (WFP), where she conducted and implemented research in Burkina Faso studying the effect of increased energy density of porridges on total energy and nutrient intake in young infants.

After obtaining her master's degree in 2014, she decided to start her PhD research project early 2015 at the department of Value-Based Healthcare/ILD Center of Excellence, at the St. Antonius Hospital (Nieuwegein) under supervision of prof. dr. Jan Grutters, prof. dr. Douwe Biesma, prof. dr. Philip van der Wees and dr. Paul van der Nat. In 2015 she received the Research Support grant from the Dutch Sarcoidosis Patients Society (Sarcoïdose Belangenvereniging Nederland) to support her research-project. In September 2016 she started a Postgraduate Epidemiology Master within the Graduate School of Life Sciences at the Utrecht University, which was completed in 2019. During her PhD, she was an active board member of "JongSTZ" and was one of the two initiators of "JongAntonius", which was founded in August 2017. In 2019, Nynke was selected by the Harvard Business School to take part in the Value-Based Health Care Delivery intensive seminar. Nynke currently works at the RIVM as an epidemiologist at the department of healthcare associated infections and antimicrobial resistance.

PHD PORTFOLIO

This is a summary of the PhD training and academic related activities.

Promotors:	prof. dr. J.C. Grutters prof. dr. D.H. Biesma prof. dr. P.J. van der Wees
Copromotor:	dr. P.B. van der Nat

Activity	Year(s)	Workload (ECTS)
Courses		
Presenting in English	2015	0.5
Cochrane systematic review	2015	0.3
Basic course SPSS	2016	0.5
Linear mixed modelling	2018	0.5
Modern methods	2016	4.5
Classical methods	2016	6
Missing data	2017	1
Molecular epidemiology of infectious diseases	2017	1.5
Epidemiology of infectious diseases	2017	1.5
Mathematical modeling of infectious diseases	2017	3
Study design in etiologic research	2017	3
Introduction to statistics and SPSS	2017	1.5
Clinical epidemiology	2017	1.5
Nutritional epidemiology	2018	1.5
Methodology in health economic evaluation	2018	1.5
Generalized linear models	2018	1.5
Survival analysis	2018	1.5
Symposia, congresses & seminars		
ERS Congress (poster x2)	2015, 2016, 2017	0.9
Jules van den Bosch Symposium	2015, 2016, 2017	0.9
Meetbaar Beter symposium	2015, 2016, 2017	0.9
EMGO+ Annual Meeting / CaRe Day	2015	0.3
NFU-expertisenetwerk selecteren en analyseren van kwaliteitsindicatoren	2015	0.3
Erasmus MC Symposium Quality of Care	2015	0.3
IQ Healthcare conference	2016, 2017, 2018	0.3
ICHOM congress	2016	0.3
VBHC seminar Maasstad Ziekenhuis	2016	0.3
Meetbaar Beter symposium	2016	0.3
ILD care Foundation	2016	0.3
VBHC Prize event	2017	0.3
Value in Care	2017	0.3
ILD care Foundation	2017	0.3
PhD retreat Radboud UMC	2017	0.3

Zorg voor Verbetering Santeon	2017	0.3
Uitkomsten van onze Zorg symposium (oral)	2017	0.8
Academic event St. Antonius (poster, oral)	2015, 2017	1.6
Clinical endpoints in sarcoidosis meeting Chicago by the Foudation for Sarcoidosis Research (oral)	2018	0.8
Harvard Business School Value Based Health Care Delivery Intensive Seminar (oral)	2019	1
<hr/>		
Teaching & supervising		
Ruben Korte (masterthesis, Erasmus University)	2015	0.5
Joelle Sillevs-Smit (research project)	2016	0.5
Koray Parmakzis (masterthesis, Erasmus University)	2017	0.5
<hr/>		
Other	Year	
Board member JongSTZ	2015-2019	3
Member JongeZorgDenkTank (JZDT)	2015-2018	2
Cofounder / board member JongAntonius	2017-2019	2
Editorial member Loupe, scientific journal St. Antonius	2016-2019	1

DANKWOORD

It giet oan! Oftewel: het gaat gebeuren! Het gaat door! Alle Friezen die dit lezen denken dan aan een Elfstedentocht. Nee, het gaat nu om de mijlpaal rondom de officiële afronding van mijn proefschrift. De Elfstedentocht kan echter wel gezien worden als metafoor voor een promotietraject. Het is vallen en opstaan, samen en alleen. Er is passie en verbroedering. Het is soms afzien en er is plezier. Er is persoonlijke groei. En dan is de finish inzicht! *Bjusterbaarlik bliid, ik haw it helle!*

Tijd voor bezinning en een terugblik op de jaren die achter mij liggen sinds ik ben begonnen met het promotieonderzoek dat heeft geleid tot dit proefschrift. Dit proefschrift was nooit tot stand gekomen zonder hulp en onvolwaardige steun van mijn promotoren, copromotoren, andere begeleiders, collega's, familie en vrienden. Hierbij wil ik graag een aantal personen in het bijzonder bedanken die hebben bijgedragen aan de totstandkoming van dit proefschrift.

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Because we are your friends

You'll never be alone again

Well, come on, well, come on, well, come on

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