SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2025; 42 (3): 16968 DOI: 10.36141/svdld.v42i3.16968 - Mattioli 1885

SUPPLEMENTARY FILE S1

2011 WASOG Task force, SCOUT, and Reported Endpoint Results

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Over the past 20 years, the number of clinical treatment trials for sarcoidosis has increased. The current World Association of Sarcoidosis and Other Granulomatous disease (WASOG) Clinical Trial Endpoint Task Force is an update of the 2012 published WASOG Endpoints for Clinical Trials in Sarcoidosis (1). The 2012 Task Force pulmonary group concluded that the forced vital capacity (FVC) was validated, reproducible, low cost, safe, and tested in sarcoidosis clinical trials. However, it was not sarcoidosis specific, and there was no reported association with quality of life. Furthermore, the committee also recommended that composite endpoints be developed. Subsequently, the Sarcoidosis Clinical Outcome Taskforce (SCOUT) published core outcome sets (2) which included physiology/clinical, quality of life, and treatment.

Since the turn of the century, both the number of intervention studies for symptomatic pulmonary disease and patient participants have increased (Figure 1). Furthermore, Figure 2 lists the multiple endpoints evaluated in the 15 placebo-controlled treatment trials of 769 patients (3). The figure shows the most common endpoints reported for each of the studies, with the FVC being reported in 13 of 15 studies. In addition to the range of reported endpoints, the figure emphasizes the lack of one single endpoint being common to all investigations. The analysis of the placebo arm from several of these trials found that FVC% predicted changed by as much as 2% during the course of study (3). Analysis of the four placebo trials which included a prednisone withdrawal scheme using a specified protocol revealed that 33-58% of placebo-treated patients reduced prednisone dosage, but less than 10% of patients totally discontinued prednisone (4-7). The goal of the current task force is to develop consensus on clinical trial endpoints for patients with pulmonary or cardiac sarcoidosis.

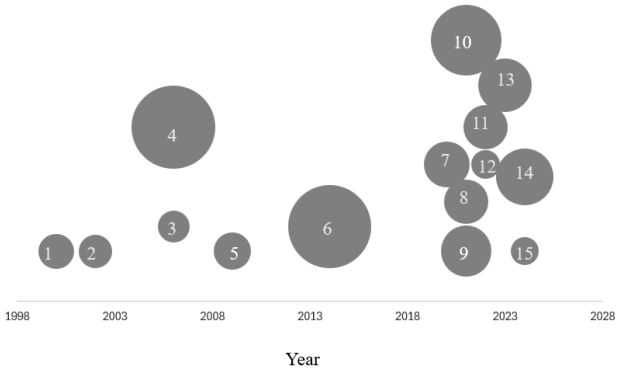

Figure 1: Double-blind, placebo controlled pulmonary sarcoidosis trials completed since 2000. The larger the bubble, the more patients enrolled.

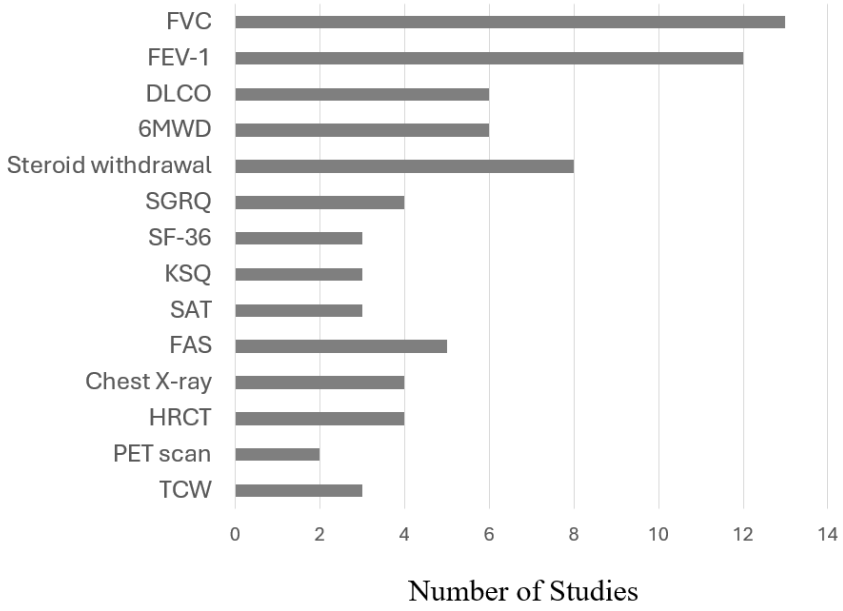

Figure 2. The clinical trial endpoint studied in 15 placebo controlled trials for pulmonary sarcoidosis since 2000. These 15 studies evaluated 769 sarcoidosis patients. FVC: force vital capacity; FEV-1: forced expiratory volume in one second; DLCO: diffusion lung of carbon monoxide; 6MWD; six minute walk distance; SGRQ: Saint George Respiratory Questionnaire; SF-36: short form 36; KSQ: Kings sarcoidosis questionnaire; SAT: sarcoidosis assessment tool; FAS: fatigue assessment scale; HRCT: high resolution computer tomography; PET: positron emission tomography; TCW: time to clinical worsening.

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Study design and endpoints

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The key consideration in determining an endpoint while designing a study for an orphan indication like sarcoidosis is the sample size required to evaluate the endpoint. The sample size must be feasible to enroll.

Of the four factors that impact sample size, the two factors that can be manipulated to change the sample size are the variability (e.g. σ or SD, the standard deviation for normal distributions) and the treatment effect (d) between dose groups (Table 1).

Endpoints with a narrow SD are preferred. Forced Vital Capacity (FVC), for example, can be evaluated as a continuous endpoint (difference between group means) or as a dichotomous (responder) endpoint (difference between group proportions). For continuous or ordinal data, between group means has less variance and therefore a smaller sample size than between group proportions and is therefore preferred (1,2).

The value for the treatment effect, typically, comes from regulatory guidance or a precedent (competitor's label). When no precedent exists and in difficult-to-enroll indications such as sarcoidosis, it may be better to first estimate a feasible sample size and then back extrapolate the treatment effect based on the sample size. Terms such as Minimal Clinically Important Difference (MCID), Clinically Important Difference (CID) are best avoided as they are used inconsistently – sometimes in the context of treatment effect, while in other instances as a meaningful within-patient threshold change (e.g. KSQ MCID) (3)

FDA's Patient-Focused Drug Development (PFDD) Guidance 4 (Draft) mentions two other terms in the context of evaluating the Meaningful Change Threshold (MCT) in Clinical Outcome Assessments (COA). The terms are Meaningful Score Difference (MSD) and Meaningful Score Regions (MSR) (2). MCTs are to be validated independently when used in the context of the treatment effect or a within-patient change.

Independent of the sample size there are other important considerations for the end point. The choice of the end point also depends on the indication – is the endpoint intended for the evaluation of a first or second (add on) line intervention or in the setting of a steroid replacement indication? It will be immensely helpful if WASOG recommendations for endpoints for anti-inflammatory therapy in pulmonary sarcoidosis specified the indication for which the end point was applicable.

WASOG recommendations on MCT for endpoints must take into consideration whether the Clinical Outcome Assessment is ordinal or continuous and validated to regulatory standards. When the COA is ordinal, a change from 4 to 8 may not be the same as a change from 5 to 9. Likewise, the MCT may be different for an increase versus decrease.

The FDA PFDD Guidance 4 is a useful document that can guide WASOG in their current recommendations and provide direction for future research (2).

aTyr Pharma is encouraged that WASOG put together a task force and invited representatives from industry, patient advocacy and key opinion leaders to voice their thoughts. It is hoped that the endpoint recommendations from WASOG will pave the way for more clinical trials towards regulatory approvals for this large unmet need.

Table 1 Factors Impacting Sample Size

Factor	Value
α - type 1 error	Fixed at 0.05
β - type 2 error	Fixed at 0.10
σ - measure of variability	Sample size is directly proportional to σ
d - treatment effect (between groups)	Sample size is inversely proportional to d

Power, 1 - β is usually 90%; when data is normally distributed σ is the standard deviation (SD)

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Sarcoidosis clinical trial design: Industry Considerations on Endpoints in Sarcoidosis

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Endpoint selection is paramount to the success of a clinical development program. Ultimately, endpoints must reflect patients' symptoms, daily function, and overall survival; however, the heterogenic presentation and variable natural disease progression make endpoint selection in sarcoidosis particularly challenging. This increases risk and creates a barrier to entry for drug development in sarcoidosis. It is therefore of the utmost importance that sarcoidosis providers, patients, advocates, industry representatives, and regulators align on endpoint selection for sarcoidosis to pave the way for future therapies.

From the perspective of industry, endpoint selection must prioritize the regulatory principle of clinical meaningfulness, while also considering statistical feasibility, as well as payer considerations to support eventual market access. Within sarcoidosis, endpoints centered around imaging (standardized uptake value [SUV] Max), lung function (forced vital capacity [FVC]), corticosteroid reduction, quality of life, and/or a composite endpoint have all been considered.

Our team compared regulatory opinion with current literature and industry opinion to identify areas of alignment or divergence for two endpoint options: corticosteroid reduction and FVC.

Regulators, providers, and industry opinion align on the clinical meaningfulness of corticosteroid reduction. However, gaps remain regarding how and when to capture this change.

Figure 1. Corticosteroid Reduction

	Regulatory Opinion (1)	Provider Opinion (2,3)	Industry Opinion	Alignment
Clinical Meaningfulness	"Clinically Meaningful"	"Clinically Meaningful"	"Clinically Meaningful"	Aligned
How it was captured	"Portion of patients able to wean"	"Percent reduction of steroid dose or cumulative steroid dose"	"Proportion of patients who achieve a tapered dose of 5 mg;" or "Portion of patients who achieve a 50% reduction	Somewhat aligned
When it was captured	"Sufficiently far from randomization"	"Symptoms of prolonged steroid use can be intolerable"	Variable	Not aligned

There was no alignment across categories for FVC. Regulators may see percent predicted (ppFVC) change in FVC as clinically important to sarcoidosis as a restrictive lung disease; however, recent publications (8), outlines phenotypic racial and gender differences in lung function which would potentially confound this. There is a lack of consensus or alignment on when lung function should be captured and how it should be used to inform treatment decisions.

Figure 2. Forced Vital Capacity

	Regulatory Opinion (1)	Provider Opinion (2,3)	Industry Opinion	Alignment
Clinical Meaningfulness	"Clinically relevant for restrictive lung disease"	"May not be adequately sensitive for anti-inflammatory therapy" "Racial and gender phenotypes confound selectin of FVC as a way to evaluate therapy response"	Variable	Not aligned
How it was captured	ppFVC	Variable	Variable	Not aligned
When it was captured	Not noted	Variable	Variable	Not aligned

Challenges of unaligned endpoint selection create barriers for both current and potential drug developers from entering the sarcoidosis clinical trial space. From the perspective of industry drug developers, it is paramount that there is alignment with the therapeutic community regarding which endpoints are clinically meaningful as well as how and when the endpoints are captured. At this time, corticosteroid reduction provides the most feasible option for drug developers that aligns with clinically meaningful outcomes valued by providers.

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Patient Recruitment Based on the EFZO-FIT Trial, the Largest Sarcoidosis Study Conducted to Date.

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The EFZO-FIT trial, which stands as the largest interventional sarcoidosis study to date, has achieved a significant milestone by successfully enrolling 268 patients. Efforts included engaging 315 potential investigative sites to initiate 104 sites across 10 different countries. Despite these efforts, 19 sites ultimately did not enroll any patients. While this enrollment number is a notable achievement, several challenges were encountered throughout the trial. These hurdles primarily revolved around site activation, patient recruitment, and enrollment. The limited number of prior sarcoidosis trials meant many investigators lacked experience in this specific area and reference data to use for study projections to inform on the number of sites and timeline needed for recruitment. Delays in site activation stemmed from the necessity to engage a large number of global sites to meet the study enrollment targets. The strain on institutional resources caused by the backlog of clinical trials after the pandemic further exacerbated these delays. Enrollment obstacles were largely attributed to lack of study prioritization, stringent inclusion/exclusion criteria outlined in the protocol, the considerable patient burden associated with monthly infusions and steroid tapering, high turnover among institutional staff, and resource constraints. Despite a substantial financial investment in patient recruitment marketing, the majority of patients were recruited through sites' internal databases; marketing efforts only accounted for 17 patients. Key strategic initiatives aTyr put in place to enhance clinical trial recruitment included the following actions: conducting onsite visits with investigators and staff, organizing interactive investigator meetings, webinars, local physician dinners, and engagement at industry meetings. The top reasons for protocol enrollment obstacles were due to inclusion criteria, such as OCS and biopsy requirements, and exclusion criteria like treatment with biological immunomodulators or conditions like extrapulmonary, ocular and cutaneous sarcoidosis. Strategies that proved effective in boosting enrollment included sites where there was close networking between investigators and local pulmonologists and advocacy groups, extensive utilization of internal patient databases, dedicated time from investigators and staff for patient education, and proactive pre-screening of potential participants. Ultimately, the success of enrollment hinged on a comprehensive

understanding of the protocol and patient population, coupled with unwavering investigator commitment and engagement. Sarcoidosis remains a high unmet medical need, with limited treatment options with acceptable safety profiles. Moving forward, we can improve patient recruitment and enrollment rates in future trials by proactively addressing the issues we encountered. This will ensure the successful completion of clinical research in sarcoidosis and allow us to improve outcomes for those affected by this challenging disease.

Patient perspectives: what do we want in Europe?

Filippo Martone

In my role as a representative of associations for people affected by sarcoidosis, I have conveyed the perspective of those suffering from this disease regarding the clinical endpoints of clinical trials.

In a study published in 2018, following a survey conducted in major European countries and the USA by associations affiliated with the Sarcoidosis Patients Advisory Group under the aegis of the European Lung Foundation—and coordinated and authored by members of the ERS Task Force dedicated to revising sarcoidosis treatment guidelines—patient priorities for treating their disease were highlighted as early as then (1). In particular, maintaining quality of life and ensuring a multidisciplinary approach to patient care were identified as fundamental factors.

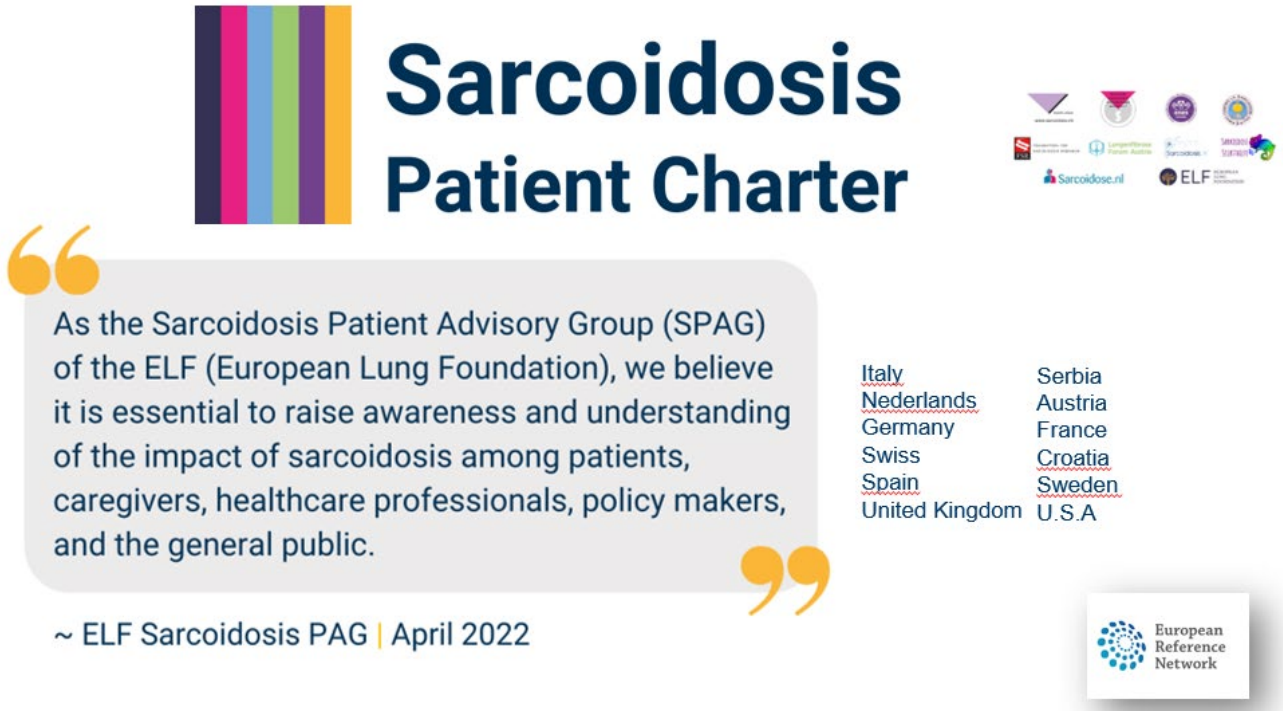
To address the unmet needs of people with sarcoidosis today, it is essential to consider certain pathological conditions when determining endpoints for clinical research trials. These include:

- **Pain**, which can be appropriately measured in terms of both type and intensity.
- **Psychological impairment**, also measurable in terms of type and severity.
- **The presence of sleep-related respiratory disorders and fatigue**, both of which are crucial, especially when measured together, to truly distinguish the impact of the proposed therapy.
- **Social and work-related ability**, which are equally measurable and significant for those suffering from chronic sarcoidosis (2).

Finally, but no less importantly, it is crucial to assess the long-term effects of proposed therapies compared to currently available treatments, such as steroids, anti-TNFalpha, immunosoppressant, etc.

It remains fundamental to emphasize that, to this day, there is a lack of reliable disease biomarkers. Such biomarkers would facilitate both clinical research and the diagnosis and follow-up of patients.

Figure 1



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Patient perspective: what do they want in America?

Andrea Wilson

Prednisone is a powerful corticosteroid commonly prescribed for conditions like sarcoidosis and other inflammatory disorders. While effective, its long-term use presents significant risks requiring very careful management and monitoring. Used in acute cases it can be lifesaving, used long – term prednisone can have the opposite effect. Understanding these risks and exploring alternative treatment options can help improve patient outcomes and quality of life.

Prolonged use of prednisone can lead to a wide range of adverse effects, including:

Steroid Toxicity: Long term use can lead to depression, agitation, elevated blood pressure and heart rhythm disturbances

Osteoporosis and Bone Loss: Long-term steroid use depletes bone density, increasing the risk of fractures. Patients should consider calcium and vitamin D supplementation to help mitigate this effect. In some cases, bone-building medications like bisphosphonates may be necessary.

Metabolic Effects: Prednisone can contribute to weight gain, diabetes, and insulin resistance. Patients should have their blood glucose levels regularly monitored to check for any early signs of metabolic trouble.

Cardiovascular Risks: The drug can elevate blood pressure and contribute to hypertension, increasing the risk of heart disease over time. A healthy lifestyle, a nutritious diet and exercise, can help reduce these risks.

Susceptibility to Infections: As an immunosuppressant, prednisone weakens the immune system, making individuals more vulnerable to infections.

The Role of Steroid-Sparing Treatments

Given the significant risks associated with prolonged prednisone use, many physicians are opting to include alternative treatments to reduce dependency on corticosteroids.

Immunosuppressive Drugs: Medications such as methotrexate, azathioprine, or mycophenolate mofetil can help control inflammation while minimizing steroid over exposure.

Biologic Therapies: Some patients may benefit from biologic agents that target specific pathways in the immune system, offering a safer long-term treatment option.

Lifestyle Modifications: A well-balanced diet, regular weight-bearing exercise, and stress management techniques can play a vital role in reducing inflammation and maintaining overall health.

Conclusion

While prednisone remains an effective treatment option for many conditions, its long-term use carries substantial risks that should not be overlooked. Patients should be educated on the importance of proper supplementation, regular health monitoring, and the availability of steroid-sparing alternatives.

Steroid Stewardship in Pulmonary Sarcoidosis

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Oral glucocorticoids (OCS) are historically a foundation for the management of pulmonary sarcoidosis based on efficacy, low cost, ease of use and healthcare provider familiarity with OCS prescribed for other common inflammatory conditions, such as asthma. Numerous studies conducted over a span of 4 decades (1960's-2000's) have demonstrated improvements in pulmonary sarcoidosis disease activity following OCS treatment, compared to untreated controls, in terms of objective increases in pulmonary function parameters, such as forced vital capacity (FVC) and diffusion capacity for carbon monoxide (DLCO), and subjective improvement in radiographic lung disease manifestations (1,2). However, pulmonary sarcoidosis disease activity recurs following OCS cessation in 20-80% of cases (1), often leading to resumption and long-term maintenance of OCS treatments in these patients.

Medium to long-term exposure to OCS, even at low doses, is fraught with numerous complications. These complications range from self-limited symptoms, such as disturbed sleep or altered mood, to potentially irreversible complications, including serious cardiovascular events (ischemic heart disease, atrial fibrillation, etc.), diabetes mellitus, osteoporosis and others (3-5). Consequently, healthcare experts seek to balance the short-term benefits of OCS, namely rapid and effective resolution of granulomatous inflammation, against the adverse complications associated with reliance on OCS to mitigate pulmonary sarcoidosis symptoms and organ damage.

To this end, the WASOG Workshop on Clinical Trial Endpoints for sarcoidosis, engaging a global panel of sarcoidosis experts, developed OCS stewardship goals and clinical guidance to optimize the management of OCS for pulmonary sarcoidosis patients. To reduce overall exposure to OCS and related toxicity the stewardship team aims to provide guidance as to reducing reliance on OCS for management of chronic sarcoidosis. On behalf of patients who are

thoughtfully considered to benefit from OCS treatments, stewardship guidelines will elucidate both short-term OCS side effects and long-term toxicities with the overall goals of reenforcing strategies to minimize OCS exposure and to achieve discontinuation of OCS. In many cases involving long-term use of OCS, even at lower doses (e.g., 5 mg daily) it can be a challenge to wean OCS due to steroid dependency or adrenal insufficiency. Therefore, the stewardship team will provide recommendations for OCS weaning, discontinuation and subsequent monitoring based on established guidelines (5). Once the goal of OCS liberation is achieved, it will be important to inform patients and practitioners of the risk of adrenal insufficiency or life-threatening adrenal crisis, especially in response to acute systemic stress (e.g., psychological stress, major surgery, severe infections), for at least one year following liberation from OCS (5-7).

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Sarcoidosis patients exposed to steroids suffer significant adverse effects

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Steroids are the most widely prescribed therapy for sarcoidosis. While effective at controlling granulomatous inflammation, they have a wide range of harmful side effects. We prospectively collected a sample of 1937 sarcoidosis patients through an international with respondents from 34 countries to investigate the association of steroid exposure with development of steroid toxicity in sarcoidosis patients. The cohort was primarily from the USA (44%), Italy (21%) Germany (9%), Netherlands (5%), and Spain (5%). The sample was analyzed with propensity matching utilizing greedy 1:1 matching without replacement. When comparing patients who had ever taken steroids to those who had never taken steroids we identified significant differences in the development of hypertension (OR 1.6 95% CI 1.0-2.6), hyperlipidemia (OR 2.5 95% CI 1.5-4.3), osteoporosis (OR 5.0 95% CI 2.8-9.3), sleep disturbances (OR 2.4 95% CI 1.5-3.9), mood changes (OR 2.8 95% CI 1.7-4.5), GERD (OR 1.8 95% CI 1.1-2.8), bruising (OR 2.4 95% CI 1.4-3.9), and new infections (OR 3.0 95% CI 1.7-5.3). We only identified differences in bruising (OR 1.8 95% CI 1.4-2.3) and cardiovascular disease (OR 1.3, 95% CI 1.01-1.8) when comparing those currently taking steroids to those not currently taking steroids. These results suggest that exposure to steroids is associated with development of significant adverse effects that do not resolve with the cessation of treatment. Future work to identify efficacious treatments for sarcoidosis that reduce dependence on oral corticosteroids is necessary.

Upending the Glucocorticoid (GC) Paradigm in Sarcoidosis: Measuring change in GC toxicity in clinical trials

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Despite the universal phenomenon of GC toxicity in sarcoidosis, there has been no practical, reliable means of calculating the degree to which GC toxicity worsened or improved has improved in clinical studies and trials. The potential impact of a new medication on reducing the impact of GC toxicity has typically been estimated only crudely (e.g., by pill-counting). A goal novel therapies for sarcoidosis is to diminish toxicity in clinically important ways, thereby differentiating new treatment approaches from current standards of care. GC toxicity has been accepted as part of the patient experience – a necessary evil - for too long in sarcoidosis. It is time to acknowledge it, measure it, and change it.

The Glucocorticoid Toxicity Index (GTI), developed by an international group of subspecialty experts as a clinical outcome assessment, is the first standardized, validated measure of GC toxicity [1]. The instrument's purpose is to measure **change** in GC toxicity: for example, between baseline and the primary endpoint. The instrument is designed to quantify both worsening and improvement in GC toxicity.

The nine domains of the full GTI are shown in **Table 1**. Domain selection was based on four principles; namely, that the GC toxicity represented by the domain is: 1) common; 2) important to both providers and patients; 3) independent from other domains; and, 4) dynamic (likely to change over time – either to worsen or to improve – with varying GC dosing). The domains selected were subdivided into independent items, which were then weighted through multicriteria decision analysis, facilitated by 1000Minds software. The GTI was then validated in a series of clinical studies [2,3] and clinical trials [4].

Two scores, the Cumulative Worsening Score (CWS) and the Aggregate Improvement Score (AIS), are derived from the same set of data recorded by investigators [1]. The instrument was designed for ease of use: investigators simply record data and the scores are calculated automatically by a digital platform. Six of the 9 domains require no input from clinicians. The other three domains require simple history and physical examination assessments.

The GTI was first licensed for a pivotal trial in ANCA-associated vasculitis [4]. The instrument was essential to demonstrating not only that treatment with the investigational treatment was associated with less GC use but also that this protocol mandated difference in GC use was associated with less GC toxicity. At both 13 and 26 weeks, avacopan demonstrated reduction in GC toxicity as measured by the CWS and AIS. The performance of the individual domains [5] and of an abridged version of the instrument focusing on metabolic domains [6] were examined in separate publications.

The STOX (Steroid Toxicity) suite of clinical trial outcome measures has now been licensed for use in 31 disease indications and employed at more than 2,000 clinical trial sites around the world. The instruments have also been used in health economic outcomes research studies. Phase 3 trials in giant cell arteritis, polymyalgia rheumatica, and IgG4-RD will report their data in 2025 or early 2026. Drug developers are encouraged to employ the GTI and related instruments in early-phase trials, gathering data to support label-enabling trials with the intention of including reduction in GC toxicity in the medication label.

TABLE 1. Domains of the Glucocorticoid Toxicity Index [1].

- Body mass index
- Blood pressure
- Glucose tolerance

- Lipid metabolism
- Bone mineral density
- Infection
- Glucocorticoid myopathy
- Skin toxicity
- Neuropsychiatric effects

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Clinical Outcome Delphi

Jan Grutters (1)

1.

New drugs are required to treat patients with sarcoidosis, especially those who have been prescribed corticosteroids (CS) over a long period and therefore risk toxicity.

Future, well-designed clinical trials with these novel drugs should include clear trial endpoints.

The aim of the current study was to develop consensus for clinical study endpoints for pulmonary sarcoidosis trials of potential drugs to reduce and/or replace treatment with CS.

A consensus-building three-round Delphi survey was carried out. In the first round, statements concerning potential endpoints were determined which were subsequently anonymously rated by an Expert panel of 30 sarcoidosis investigators in Round 2. In the final Round 3, these 97 statements were evaluated on a 5-point Likert-scale by the Expert panel and also by 70 stakeholders, including health care providers, sarcoidosis patients, as well as representatives from industry. Consensus was a priori defined as 70% of all responders.

The Expert panel reached consensus on 38 statements including prednisone reduction by 50%, discontinuation of prednisone, 10% predicted or greater improvement in FVC%, FEV_1%, and DLCO% predicted, improvement of at least 4 points on the subscale ‘Lung’ and 8 points on the subscale ‘General health’ on the Kings Sarcoidosis Questionnaire (KSQ). The Expert panel also reached consensus supporting combination endpoints: a composite endpoint that included prednisone tapering, improvement of FVC and improvement in a quality-of-life measure. The majority of stakeholders agreed to all statements.

This Delphi survey reached consensus concerning several specific endpoints for studies of novel drugs for symptomatic pulmonary sarcoidosis patients which are currently on CS.

Pulmonary assessment: Pulmonary Function Testing and Symptoms

Dan Culver (1)

Pulmonary physiology measurements have been used to define study populations (entry criteria) as well as endpoints. The study population should select a group of patients that may be expected to benefit from the proposed intervention, can safely participate in a trial that involves placebo, will not be likely to have intercurrent events that disrupt adherence to the protocol for the duration of the trial, and that have physiologic function in a range wherein ceiling or floor effects are less likely.

For pulmonary function tests (PFTs), these considerations have typically resulted in exclusion of patients with more preserved spirometry (in most but not all studies) and also of patients with more severe disease, often defined as forced vital capacity less than 50% predicted or FEV1 below 50-60% (1,2). Reference values may disenfranchise some groups if race-based % predicted values are used to determine trial eligibility (). Also, some patients may start with spirometric values more than 100% (theoretically 50% of the population), so that FVC of 95% may be extremely abnormal if premorbid baseline was 130%, for example.

Study populations can be narrow or broad. In general, they are designed to mirror the intended use that will be listed in the regulatory label, especially in later trial stages. Using pulmonary physiology to define narrow or broad trial populations therefore will have trade-offs: narrow populations have improved signal to noise ratio (lower beta-error rate and small sample size needed); broader populations will require a larger number of enrollees but will also have more applicability to a larger proportion of the total sarcoidosis population and may enroll quicker.

The trial design itself influences how PFTs are used (as continuous or threshold measurements), and perhaps also what the clinically meaningful threshold should be. For example, an event-based trial such as time to clinical worsening will require a pre-defined threshold but a trial

evaluating change in 6 MWD could evaluate the effect as a continuous outcome variable, a more powerful statistical approach.

Other than six minute walk distance, PFTs are currently viewed as surrogate endpoints. PFTs have weak-to-moderate correlation with patient symptoms and function (4,5). They are not helpful over the duration and size of a feasible clinical trial to inform mortality prediction. Further longitudinal cohorts will help illuminate the relationship of changes in PFTs with outcomes directly to relevant to patient functioning or quality of life. Novel application of techniques like oscillometry may also allow more sensitive evaluation of change.

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Pulmonary Function Phenotypes

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Introduction: As we approach selection of pulmonary sarcoidosis clinical trial endpoints, it is important to consider the heterogeneity of pulmonary sarcoidosis. Historically, the primary physiologic pulmonary endpoint chosen for sarcoidosis has been the forced vital capacity (FVC). However, recently more research has shown that this physiologic endpoint is not significant for all individuals.

Discussion: Several publications have described physiological phenotypes in sarcoidosis in addition to the typically described restrictive phenotype. A combined obstructive restrictive phenotype has been described by multiple groups and noted be enriched for individuals with fibrocystic disease (1,2). Additionally, an obstructive phenotype has been described with association with parenchymal nodular disease on imaging (2,3). While there is consensus among the experts that pulmonary function phenotype when considering clinical trial endpoints, it is recognized that there is a lack of data on the biologic underpinnings of phenotype and the association with clinically meaningful outcomes to patients. Historically physiologic measures in sarcoidosis have been poorly associated with patient reported outcomes (4), however the lack of correlation may be due to lumping all patients together instead of splitting by phenotype. While it is clear that one physiologic spirometry endpoint does not encompass all of the heterogeneity in pulmonary sarcoidosis, the story still remains on whether there is another physiologic measurement in sarcoidosis that has yet to be discovered.

Conclusion: Pulmonary function phenotypes should be considered when selecting clinical trial endpoints for pulmonary sarcoidosis. More work is needed to understand if there are other physiologic endpoint beyond spirometry and diffusion capacity that would be ideal in pulmonary sarcoidosis.

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Clinical Trial Endpoints in Sarcoidosis: HRCT

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When considering imaging endpoints in diffuse interstitial lung diseases (DILDs), high-resolution computed tomography (HRCT), unlike plain chest radiography (CXR), has the advantage of superior contrast resolution and absent anatomical superimposition. Not surprisingly, individual patterns of lung disease are depicted in greater detail which, given the multitude of HRCT signs/patterns — quantified for extent and/or severity — might serve as imaging-based endpoints in clinical trials in sarcoidosis. That said, in a Delphi review, there was no expert consensus on clinically important imaging endpoints (whether on CXR or HRCT) although a broad trend towards disagreement for CXR and towards agreement for HRCT has been documented.

The traditional means of reviewing HRCT in research or clinical studies has been visual assessment. This has the advantage of relative simplicity, speed and low cost but is beset by issues of inter- and intra-observer variability. Accordingly, it seems likely that, in the era of artificial intelligence (AI) and machine learning (ML), automated quantification will play an increasing role. Indeed, *unsupervised* AI/ML has the potential to unravel features on HRCT 'hidden' to the human eye (1,2,3).

Irrespective of the means of assessment, consideration must be given to i) standardisation of technical parameters (principally, CT slice thickness [≤1.5 mm]), reconstruction algorithm, volumetric acquisition [as opposed to inter-spaced], and dose) and ii) radiologic terminology — non-standard (i.e. non-Fleischnarian) radiologic descriptors are best avoided (4,5). To date there are little or no data from serial CT studies in sarcoidosis on the validity of HRCT endpoints for clinical trials. That said, evidence from CT studies in DILDs, including sarcoidosis, have shown that specific morphologic features at a single time-point may have important functional and/or prognostic significance: for instance, the physiologic / prognostic impact of total disease extent, honeycombing and traction bronchiectasis or traction bronchiolectasis has been consistently highlighted (6,7,8).

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Mortality & Significant Morbidity Predictors as Endpoints in Pulmonary Sarcoidosis Clinical Trials

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Five to nine percent of patients with sarcoidosis die from their disease (1). Mortality is highest in Black individuals (12- to 14-fold higher than other racial groups), females (1.5-fold higher), and in older age patients (2,3). Pulmonary fibrosis and sarcoidosis associated pulmonary hypertension (SAPH) are the strongest mortality predictors in pulmonary sarcoidosis (1,2,4). Kirkil and colleagues found a 3-fold higher mortality in patients with more than 20% fibrosis versus those with less (1) and more recently, we showed that amongst patients with fibrotic pulmonary sarcoidosis (FPS), the extent, distribution, and patterns of fibrosis on high resolution computed tomography (HRCT) scans were associated with increased mortality (5). Presence of basal subpleural honeycomb cystic changes was associated with the highest mortality (aHR 7.9) and the worst pulmonary function (mean FVC < 60% and DLCO<40%) (5). DLCO < 40% was an independent mortality predictor however, other studies have found that FVC < 2.5L (6) and a mixed obstructive and restrictive ventilatory defect (7) are also independent mortality predictors in patients with pulmonary sarcoidosis. Presence of SAPH is a significant mortality predictor (4,9). Sarcoidosis patients with pre-capillary pulmonary hypertension diagnosed by right heart catheterization had a 9-fold increased risk of death in one study (1). SAPH is more likely to occur in patients with extensive pulmonary fibrosis. Our group found that over 50% of patients with > 20% fibrosis had SAPH versus 20% of those with < 10% Fibrosis (5). A predictive algorithm incorporating the composite physiologic index (defined as a composite score of FEV1, FVC, and DLCO), the HRCT extent of fibrosis and SAPH as evidenced by an increased mean

pulmonary artery to ascending aorta diameter (mPAD/AAD) on HRCT scan was shown to accurately predict mortality in pulmonary sarcoidosis (1,4,8).

Other mortality predictors in patients with pulmonary sarcoidosis include the presence and number of co-morbidities (9), hospitalization (10), and respiratory failure (10). Hospitalized pulmonary sarcoidosis patients had an all-cause mortality rate of 2.6% however, mortality was 13-times higher in those with respiratory failure (10). Table 1 summarizes the morbidity and mortality predictors in patients with pulmonary sarcoidosis.

Capturing morbidity and mortality and/or the predictors thereof (specifically the onset and/or progression of pulmonary fibrosis and/or SAPH) as endpoints in pulmonary sarcoidosis clinical trials is challenging due to the unpredictable nature of the disease and the overall rarity of these events. The inadequacy of FVC as a sole outcome predictor in pulmonary sarcoidosis has been emphasized elsewhere in this paper. Though the presence of fibrosis on chest roentgenogram and HRCT have been associated with increased mortality (1,4,8) changes in radiographic images are not sufficiently sensitive as outcome measures in clinical trials (11). Composite outcome measures incorporating carefully selected parameters designed to capture disease progression, clinical decline, and/or mortality have been proposed to capture morbidity and mortality in well-defined cohorts of sarcoidosis patients enriched with features predictive of high-risk disease (8). Time to clinical worsening (TTCW) – an outcome that incorporates time to death, lung transplantation, hospitalization, decline in FVC or six-minute walk distance has been evaluated in two studies conducted in patients with fibrotic pulmonary sarcoidosis (13) and SAPH (14) and is discussed elsewhere in this supplement.

Table 1: Summary of Morbidity and Mortality Predictors in Pulmonary Sarcoidosis

Morbidity/Mortality Predictor	Comment	Reference
Demographics	Black individuals, Females, *Older age group have higher mortality.	13,14
Scadding Stage	Higher mortality in patients with Scadding stages III and IV vs. Scadding I and II.	1
PFT Abnormalities	FVC < 60% FVC < 2.5L DLCO < 40% Mixed Obstructive and ventilatory defect	15 16 15 17
Fibrotic Pulmonary Sarcoidosis	Presence of Fibrosis HRCT Extent of Fibrosis (> 20% Fibrosis on HRCT) Pattern of Fibrosis (Fibrocystic changes, large bullae) Distribution of Fibrosis - Basal subpleural honeycomb cystic changes was associated with highest mortality.	1 1,15 15 15
Sarcoidosis Associated Pulmonary Hypertension (SAPH)	SAPH by RHC (elevated pre-capillary pressures) Echocardiographic evidence of elevated pulmonary pressures. Increased mPAD/AD on HRCT	15 2,15 2,15
Co-Morbidity Burden	Patients with higher co-morbid disease burden had higher mortality. Presence of 4 or more comorbid diseases was associated with the highest mortality.	9
Hospitalization	Hospitalized patients with pulmonary sarcoidosis had an all-cause mortality rate of 2.6%. Mortality was 13-times higher in those with respiratory failure and 26-times higher in patients who required mechanical ventilation.	8
Predictive Models	The GAP model incorporating gender, age, and Physiology (FVC, DLCO) predicted increased mortality in patients with GAP stage 3. The Walsh Algorithm incorporating CPI, HRCT extent of fibrosis and mPAP/AD > 1 performed well as a mortality predictor. Replacing the mPAD/AD > 1 with mPAD/BSA > 16 improved the predictive ability of the model.	1 1,2,8

Abbreviations defined:
PFT = Pulmonary Function test, FVC = Forced Vital Capacity, DLCO = Diffusion Capacity of Carbon Monoxide, CXR = Chest X-Ray, HRCT = High Resolution computed tomography scans, RHC = Right Heart Catheterization, mPAD/AD = main pulmonary artery diameter to aorta diameter, GAP Model = Gender, Age, Physiology, CPI = Composite Physiology Index , mPAD/BSA = main pulmonary artery diameter to body surface area. *Age adjusted models.

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Clinically meaningful serial change: cohort treatment effects and trial end-points.

Athul U. Wellls

The term “minimal clinical important difference” (MCID) has caused confusion as it can be applied to two separate scenarios.

MCIDs in trial or large observational cohorts are calculated using cohort distributional or anchor techniques (in which thresholds are defined against changes in other domains). For example, serial forced vital capacity (FVC) change in idiopathic pulmonary fibrosis (IPF) is anchored against change in symptoms or quality of life. In well-powered cohorts, MCIDs are not influenced by measurement variation: patients with overstatement of change due to measurement variation are balanced by patients with understatement of change. The MCID for FVC in IPF usually approximates 3.0-4.0% of predicted normal **(1,2)**. MCIDs are often used to determine whether differences associated with treatment are clinically significant.

The second scenario applies to individual patients. In principle, defining clinically significant change in individuals allows the prevalence of significant change to be compared between trial arms. This leads to the concept of “MCIDs in individual patients” and the misconception that cohort MCID’s can be used for this purpose. However, in individuals, ***measurement variation has a profound impact on serial change***. To be “real” and not ascribable to measurement variability, change must exceed (1.65 x the coefficient of variation) **(3)**. This equates to an FVC change of at least 8% of baseline values (i.e. a change of up to 6% of predicted normal FVC). Importantly, this threshold does not define “clinically significant change” but merely indicates that true change in that individual lies between zero and 16%. Quantifying “definite” clinically significant change in an individual requires the summation of measurement variability and a cohort MCID: this underpins analyses in clinical trials of high thresholds of FVC change in individuals (such as 10% of predicted normal values).

Accumulated experience indicates that such analyses are fatally flawed. Discriminatory information is limited to the small minority of patients crossing change thresholds and does not capture the whole spectrum of change **(4)**. Moreover, analyses limited to small patient subsets are seriously under-powered. In the pivotal IPF INPULSIS nintedanib trials, active treatment was associated with major benefits on continuous FVC change **(5):** this treatment effect

corresponds to a major increase in life expectancy **(6)**. By contrast, threshold analyses of change in FVC of 10% of predicted normal were non-significant in one trial (p=0.18) and only barely significant in the other. These observations were mirrored in the TRAIL trial of pirfenidone in rheumatoid lung **(7)**. In a pulmonary sarcoidosis trial, infliximab had no significant benefit on this FVC threshold, met by only a handful of patients **(8)**.

In summary, cohort MCIDs thresholds for FVC lie well within variation ascribable to measurement variability and have no role as primary end-points in individuals. The use of individual patient thresholds for change as primary end- points, whether MCIDs or much higher thresholds for clinically significant change, imposes an unrealistic burden on clinical trial design, and will fail to show, or hugely understate, benefits for a therapy that is truly beneficial.

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Changes in Pulmonary Function Tests as a Clinical Trial Endpoint

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Changes in pulmonary function tests (PFTs) are key endpoints in clinical trials for pulmonary sarcoidosis. According to various trials, variation in Forced Vital Capacity (FVC) % predicted is the most frequently used parameter to assess lung function improvement, with positive changes ranging from +2.1% to 11.8% in treated patients (1–4). In studies assessing the "natural decline" without treatment, sarcoidosis patients experience an annual decrease in FVC of approximately -140mL and -6% predicted (5,6).

Among PFT parameters, FVC is the most commonly used, with its changes correlating with chest CT findings (7), but probably not with quality-of-life (QOL) indicators or patient-reported outcome measures (PROMs). FEV_1 may be particularly useful for assessing obstructive conditions such as exacerbations or stenosis (1). DLCO is highly sensitive but less correlated with chest CT and can be influenced by various factors, including pulmonary hypertension. The 6-minute walk distance (6MWD) has been more recently used in sarcoidosis trials, particularly in studies on pulmonary hypertension, but it is also affected by factors beyond lung function, such as sarcopenia and cardiac failure (1). These parameters were recently ranked by experts in a Delphi study in order of importance as follows: FVC, DLCO, FEV_1, 6MWD, and FEV_1/FVC.

A major challenge in clinical trials is determining the best approach to analyze FVC changes. Assessing FVC variation using the percentage of predicted values rather than changes in milliliters allows for better comparison between studies and provides a more accurate representation of patient variability.

The timing of FVC change analysis must be carefully considered, and should align with the trial's objectives. Therapeutic effects are typically observed after six months, except for

corticosteroids (2), while corticosteroid tapering, relapse prevention, or slowing disease progression may require longer follow-up periods (8).

In the Delphi study a consensus was reached aggreging that “absolute changes of FVC of 10% or more are clinically important in symptomatic pulmonary sarcoidosis trials”. However, in some study, such as glucocorticoid tapering trial, FVC may not accurately reflect drug effects. When the tested treatment is ineffective, glucocorticoid doses may be increased, leading to apparent FVC improvement. Additionally, changes over time may depend on age, sex, function phenotype, and baseline lung function(9). While thresholds/categorical variables are easier to interpret in clinical practice, they should be used with caution even when a well-defined threshold has been established for the disease. Continuous variation is generally preferred over categorical thresholds (e.g., 5% or 10%) as it avoids bias, loss of information, improves statistical power, —similar to what has been observed in IPF trials (10)—and enhances reproducibility (11).

Overall, FVC % predicted remains a fundamental endpoint in sarcoidosis trials, but its interpretation requires careful consideration. Using continuous rather than categorical analysis may enhance the assessment of lung function changes in clinical research. However, FVC changes may not fully capture all clinical situations, such as glucocorticoid tapering or quality-of-life improvements. Therefore, incorporating FVC into a composite endpoint should be considered to provide a more comprehensive evaluation of treatment effects.

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Imaging as endpoint in pulmonary sarcoidosis clinical trials

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When considering imaging as an endpoint in pulmonary sarcoidosis clinical trials, three different modalities could be of interest. Although chest X-ray has been used for more than 6 decades, it is not considered a valuable endpoint in clinical trials based on the low sensitivity in detecting abnormalities and high interobserver variability (1). High-resolution computed tomography (HRCT) is currently widely used in diagnosis and management of patients with pulmonary sarcoidosis. A scoring system looking at nodularity, consolidations, ground-glass opafication and interlobular thickening has been developed in 2016, however, did not found its way into daily practice (2). Flourine-18 fluorodeoxyglucose Positron Emission Tomography (18F-FDG-PET) seems to be the most promising imaging tool as an endpoint in pulmonary sarcoidosis clinicial trials. FDG-PET has the highest sensitivity regarding detection of inflammatory activity in patients with sarcoidosis compared to serum biomarkers such as ACE and sIL-2R (3). Furthermore, studies in both pulmonary as well as cardiac sarcoidosis suggested a correlation between inflammatory activity at baseline (SUVmax) and improvement in either pulmonary function or cardiac function after initiation of immunosuppressive treatment, figure 1 (4,5). However, further studies are needed to clarify whether correlations exist between inflammation at baseline and improvement of function in either pulmonary or cardiac sarcoidosis. A major problem in using FDG-PET as an important outcome in clinical trials is the fact that the most sensitive readout of FDG-PET regarding the total burden of inflammation in sarcoidosis has to be identified. Small studies compared SUVmax with Total Lung Glycolysis (TLG) and found no differences in the ability to predict symptoms or response to treatment (6,7). The radiation dose using FDG-PET ranges between approximately 8 to 32 mSv depending on the protocol, with more recent protocols using the least radiation dose (8,9). Therefore, when thinking of FDG-PET as an imaging endpoint it is necessary to reduce the amount of FDG-PET scans to a minimum. While in pulmonary sarcoidosis inflammatory activity measured by FDG-PET seems to correlate with disease course or response to treatment, this is more difficult in patients with cardiac sarcoidosis. In cardiac sarcoidosis, the amount of myocardial scarring seems more associated with clinical outcome compared to the amount of inflammation in the myocardium (10).

To conclude, compared to chest X-ray and HRCT, FDG-PET holds the most promise to be included as an important secondary imaging outcome in patients with pulmonary sarcoidosis in the near future.

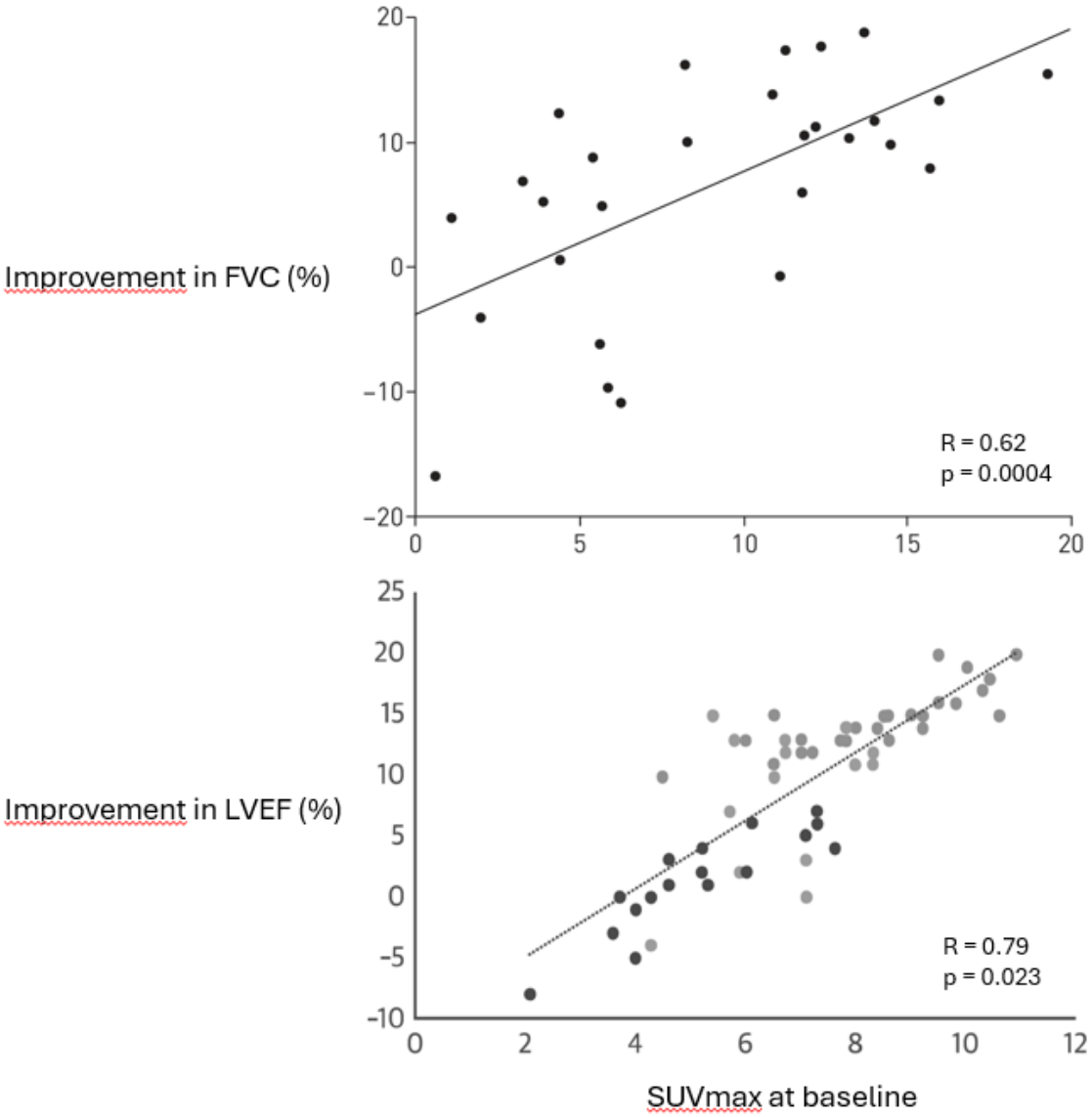

Figure 1. Correlation between SUVmax at baseline and improvement of pulmonary function and cardiac function after initiation of immunosuppressive therapy.

Adapted form (9, 10). FVC = Forced Vital Capacity LVEF = Left Ventricular Ejection Fraction. SUVmax = the maximum Standardised Uptake Value

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Changes in Health-Related Quality of Life

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Sarcoidosis has wide-ranging impacts on health-related quality of life (HRQoL), for example by causing fatigue, pain, low mood and for patients with lung disease, breathlessness and cough. From a patient's perspective, symptoms and their impact are most important and it is therefore essential to assess this on the clinic and research setting. HRQoL is one the three important FDA definitions of clinical meaningfulness; "feel, function and survive."[1] In a recent Delphi survey of sarcoidosis clinical experts, HRQoL was ranked the most important endpoint to assess Sarcoidosis treatments ahead of treatment changes (such as dose reduction), lung function and imaging.[2] The experts ranked patient reported outcome endpoints in order of importance: King's Sarcoidosis Questionnaire (KSQ)-lung, KSQ-general health, fatigue assessment scale and patient global assessment endpoints.[2] The KSQ is the most widely used disease specific health status patient reported outcome measure, it is brief and validated (lung: 6 items, general health: 10 items that includes fatigue).[3] The Sarcoidosis Assessment Tool is another validated disease specific questionnaire, also a modular structure and a total of 51 items.[4] The Meaningful Score Difference (MSD) for KSQ lung is a change of 4 units and for general health module 8 units.[5] The KSQ is responsive endpoint, in a phase two trial of Efzofitimod, the treatment benefit was a 16-unit change in KSQ-lung, considerably greater than the MSD.[6]

Whilst there has been good progress in understanding the impact of sarcoidosis on patients and development of disease specific patient reported outcome measures, more work is needed to optimize the tools from a regulatory perspective when assessing the efficacy of treatment in clinical trials. Qualitative studies (patient interviews) are needed for more detailed assessment of content

validity of KSQ and other endpoints. The Meaningful Score Difference for all endpoints needs to be determined using regulatory approved methodology. This includes the use of anchors such as patient global impression scale for health status or disease severity.[1] This is best determined in the standardized setting of a clinical trial. Further work is needed to determine the optimal tools to assess dyspnea and cough without burdening the patient with additional questionnaires. This may be achieved with numeric rating scale (NRS: 0-10) for worst breathlessness in the past 24 hours and similarly for cough severity. It is important to evaluate health economics with tools such as EQ5D.[7] The analysis of patient reported outcome measures is best done with a responder analysis rather than comparison of group means which can be influenced by large changes in a small number of patients.

Further research of patient reported outcome measures for sarcoidosis is needed and this should be in collaboration with regulators such as the FDA and EMA. As sarcoidosis is a heterogeneous condition, consideration should be given for patient reported outcome measures to be used as the primary endpoint in clinical trials to capture the impact of this multi-system condition.

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Glucocorticoid withdrawal endpoints

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Several glucocorticoid withdrawal endpoints (GWEs) could be considered for use in pulmonary sarcoidosis trials (Table 1). Because glucocorticoid use in pulmonary sarcoidosis is not standardized, it is recommended that all trials with GWEs use standardized protocols for the tapering of glucocorticoids and for the treatment of sarcoidosis relapses. Additionally, because glucocorticoid tapering might worsen pulmonary sarcoidosis if the study drug is inadequately effective, criteria for successful glucocorticoid tapering must include that the subject is not clinically deteriorating when glucocorticoids are being withdrawn. Although monitoring pulmonary function and health related quality of life may be useful guiderails to assess such clinical deterioration, no set of objective measures is likely all capture all possible causes of clinical deterioration. Therefore, the primary criterion for clinical deterioration should be based on clinician judgment, specifically the clinician's opinion that anti-sarcoidosis therapy needs to be increased.

The level of support for various GWEs for pulmonary sarcoidosis trials is also displayed in Table 1. As pulmonary sarcoidosis exacerbations rarely occur while patients are receiving $\geq$ 10 mg of prednisone/day (1), the change in the glucocorticoid dose and percentage change in the glucocorticoid dose are not attractive GWEs. Furthermore, because nearly 80% of pulmonary sarcoidosis exacerbations occur on < 5 mg of prednisone/day (1), GWEs of tapering prednisone to $\leq$ 5 mg/day or completely discontinuing prednisone are reasonable. If a successful taper of glucocorticoids to a specific daily dose or glucocorticoid discontinuation is used as a GWE, it is recommended that the subject remain sarcoidosis relapse-free for at least 3 months. Rigorous algorithms to reliably assess glucocorticoid toxicity such as the Corticosteroid Toxicity Index (2) may also be useful GWEs. Table 2 outlines necessary criteria for a GWE trial.

GWE	Issues with the GWE	Rating of the GWE Endpoint	Pulmonary sarcoidosis trial using the GWE	Reference
Change in GC dose	Small lowest effective dose is usually small such that differences from placebo group are small	+	EFZO-FIT (efzofitimod) Ustekinumab/golimumab	Ongoing trial (3,4)
% change in GC dose	Small lowest effective dose is usually small such that differences from placebo group are small	+	EFZO-FIT (efzofitimod)	Ongoing trial
Area under the daily curve of GC dose	Clinically meaningful difference is unclear	+	Efzofitimod	(4)
Lowest effective* GC dose	Limited clinical data concerning this endpoint	++	-	-
Lowest effective* GC dose < 5 mg/day of prednisone	May require a large N if a large percentage of patients fail to reach this endpoint	+++	-	-
Discontinuation of GC	May require a large N if a large percentage of patients fail to reach this endpoint	+++	NamilumaB XTMAB-16	Ongoing trials
Cumulative GC dose	Limited clinical data concerning this endpoint	+	NamilumaB XTMAB-16	Ongoing trials
Glucocorticoid Toxicity Index	Assumes a strong correlation with actual development of GC toxicity	++	NamilumaB XTMAB-16	Ongoing trials

Table 1: Potential Glucocorticoid Withdrawal Endpoints (GWEs) for Pulmonary Sarcoidosis

GWE: Glucocorticoid withdrawal endpoint; GC: glucocorticoid; *: dose below which leads to the need to increase anti-sarcoidosis therapy; +: fair; ++: good; +++: very good

Table 2: Necessary criteria of glucocorticoid withdrawal endpoint (GWE) trial for pulmonary sarcoidosis

- The glucocorticoid tapering schedule should be standardized.
- The approach to treatment of ensuing pulmonary sarcoidosis exacerbations should be standardized.
- Exacerbations of pulmonary sarcoidosis should be based on the clinician's judgment that an increase in anti-granulomatous therapy is indicated.
    - Additional criteria of a pulmonary exacerbation including patient health-related quality of life, pulmonary function tests, and other clinical parameters may also be used, but these criteria should not supplant the clinician's judgement an increase in anti-granulomatous therapy is needed.
- GWEs concerning GC tapering to a specific daily GC dose with an pulmonary sarcoidosis exacerbation should be a doses of $\leq$ 5 mg/day of daily prednisone equivalent.
    - These GWE endpoints also require that the subjects to not experience a pulmonary exacerbation on the target tapering GC doses for at least 3 months.

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Composite endpoints: Sarcoidosis Treatment Score and more

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The heterogeneity of sarcoidosis complicates endpoint selection. The WASOG task force 2011 recommended the use of composite endpoints in sarcoidosis trials, including objective measurers, which vary according to specific organ manifestations, and quality-of- life measures (1). There is no consensus on the use of composite endpoints for pulmonary sarcoidosis. Here, we highlight some composite endpoints used so far in clinical trials.

The Sarcoidosis Treatment Score (STS), developed in 2018 by using the data from a retrospective study of repository corticotropin injection (RCI) (2), encompasses forced vital capacity (FVC), diffusion capacity (DLco), high resolution computer tomography (HRCT), Kings sarcoidosis questionnaire general health (KSQ-GH), fatigue assessment scale (FAS) and steroid tapering. The STS has shown a good correlation with changes in FVC, 6-minute walk test and KSQ-GH, but not with HRCT and DLco. In another phase IV trial with RCI, STS showed to correlate with clinical response at week 24 (end of the double- blind phase) and at week 48 (end of the open-label extension phase), with a double fold increase of the score in responders compared to placebo (3). Another composite endpoint is the Time to Clinical Worsening (TCW), which includes all causes mortality, need for hospitalization attributable to progression of disease and 50m decrease in the 6MWD or worsening of WHO functional class. TCW has shown to be a viable endpoint in studies of pulmonary hypertension resulting from parenchymal lung disease, such as sarcoidosis associated pulmonary hypertension (4). In the trial of pirfenidone for progressive fibrotic sarcoidosis (PIRFS), TCW did not significantly differ between the treatment and placebo arm, but was significantly shorter in a subset of patients with reduced baseline DLco(5).

The combination of prednisolone reduction (>50%) or discontinuation, along with a decline in FVC and decrease in KSQ, is another promising approach for clinical trails in pulmonary sarcoidosis. However, uncertainties remain about the threshold of FVC and KSQ changes from baseline. Based on the results of the phase II Efzofitimob trials(6), an absolute change in FVC>5% could be considered as clinically relevant for sarcoidosis, i.e. outside of the variability range. The same trial also observed a significant increase in the KSQ lung and GH scores in the treatment arm, exceeding the MCID of 4 and 8 points respectively, compared to placebo (6), suggesting a good clinical correlation with treatment response.

The PREDMETH trial investigated the efficacy of methotrexate compared to prednisone as first-line treatment for pulmonary sarcoidosis. The non-inferiority margin was set at 5% for the between-group difference in FVC changes after 24 weeks of treatment(7). Although this trial did not use a composite endpoint, it included several secondary endpoints, such as the KSQ, to get a better understanding of treatment's effect.

The Delphi survey conducted among experts in 2024, which also included questions on composite endpoints, reached a consensus on the use of prednisolone dose reduction (>50%) or discontinuation, in combination with an <5% decrease in FVC (absolute change) and <4 points decrease in KSQ in symptomatic pulmonary sarcoidosis trials. In conclusion, the limited and variable data on composite endpoints in clinical trials for pulmonary sarcoidosis highlights the need for further research and analysis to optimize these endpoints for sarcoidosis.

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Time to Clinical Worsening: "The" Composite Endpoint

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Like in other diseases, the sarcoidosis investigative community has struggled with the identification of clinically important trial endpoints. Usually, studies have incorporated unidimensional endpoints of pulmonary function (FVC), quality of life (HRQoL), or steroid tapering. However, in isolation these endpoints have yet to capture clinically meaningful change as desired by patients and practicing physicians. Hence, as with other diseases, strategies are now focusing on combined or composite endpoints.

The concept of "time to clinical worsening" (TCW) goes by many aliases including disease free interval, time to progression, progression free survival, and time to relapse. Although many composite endpoints exist, TCW can be a favorite. By encapsulating multiple domains of disease progression and utilizing the concept of feels, functions, and survives, this composite endpoint mimics treatment changes that occur in the practice of medicine.

The usage of TCW as a primary clinical trial endpoint continues to gain popularity in many fields of medicine including malignancy, pulmonary artery hypertension, interstitial lung disease, and congestive heart failure. Two small placebo-controlled, randomized sarcoidosis clinical trials have successfully utilized TCW as a primary endpoint: Riosaph (riociguat for sarcoidosis pulmonary hypertension) (1) and PIRS (pirfinedone for fibrotic sarcoidosis) (2).

In stark contrast to unidimensional endpoints such as FVC or HRQoL, the composite endpoint, TCW can incorporate implications of survival, function, and quality of life in phase 2-3 pulmonary randomized clinical trials.

In a recent Delphi analysis, a 70% consensus was reached for 100 sarcoidosis clinical trial investigators who answered the following question: "When comparing active treatment versus placebo-treatment arms, the time to patient relapse is clinically important in symptomatic pulmonary sarcoidosis trials." However, in a subsequent question, "The time until clinical

worsening (TCW) is a clinically important endpoint in symptomatic pulmonary sarcoidosis trials", only 65% achieved agreement. So, why was consensus not achieved when the descriptor time to patient relapse was replaced by the terminology TCW? Perhaps this reflects investigator difficulty with the TCW concept and the assignment of components. Although investigators recognize the concept of patient relapse as an important endpoint, determining the important composite ingredients creates difficulty.

Choosing the components of TCW requires careful thought and consideration. Although the domains can be flexible, they should always herald disease worsening while capturing the hallmarks of feels, functions, and survives. Virtually all trials should include sarcoidosis related hospitalization and disease related death. Because the most common TCW component in many other diseases, death, is an unlikely complication of sarcoidosis, incorporating it into the composite may be insensitive to intervention. However, death should be included due to its ultimate clinical significance. Furthermore, obtaining clinically meaningful FVC improvements remains challenging. Common events, such as pulmonary exacerbation requiring steroids for two weeks, should be considered. The Table reflects some potential TCW components.

Because TCW can encompass the much-desired concepts of feels, functions, and survives in a real world management setting, it remains a viable endpoint for sarcoidosis clinical trials. Its flexibility enables inclusion of components that reflect intervention outcome. Diseases, such as PAH, have evolved from unidimensional endpoints to composite TCW. Although study duration may be lengthened with TCW, the results can be more meaningful of the disease process. For example, increasing FVC% predicted by 10% may reach the threshold of statistically significant but be clinically unmeaningful when the absolute numbers range from 90-100%.

Better understanding of the importance and practicality of TCW requires two interventions. Firstly, it will be necessary to obtain consensus on steroid tapering and rescue schedules. Steroids remain a common treatment option for many sarcoidosis patients. During tapering, exacerbation leading to increased OCS can occur, and it is necessary to standardize loss of function (decreased FVC or worsened HRQol). Secondly, analysis of solitary endpoints can improve understanding of TCW. Correlating changes in function with imaging, HRQol, etc can enhance knowledge leading to new, improved clinical trial endpoints.

Table 1.

Possible Predefined TCW Components for Randomized Clinical Trials in Symptomatic Pulmonary Sarcoidosis

- **All-cause death**
- **Sarcoidosis-specific death**
- **Hospitalization for sarcoidosis**
- **Any hospitalization**
- **ER visit for shortness of breath**
- **SOB treated with increased prednisone for more than 2 weeks**
- **HR-QOL worsening**
- **FVC decrease (>5-10%)**
- **Chest imaging deterioration**

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Cardiovascular clinical and biomarker endpoint manuscript section.

Lesley T. Cooper

Cardiac sarcoidosis is a rare disorder that typically presents with high grade heart block, ventricular arrhythmias (VA) or symptomatic heart failure. The combined rates of death, heart transplant and destination ventricular assist device use are at least 2% per year. Nonfatal but clinically relevant cardiac events include hospitalizations for heart failure and ventricular arrhythmias which together with the rates of death and heart transplant are at least 5% per year.(1) More common outpatient endpoints may include sustained or symptomatic ventricular arrhythmias, urgent heart failure visits and escalation of diuretic dose for at least 7 days. All cardiovascular events are more frequent in patients with reduced left or right ventricular function, active cardiac inflammation or extensive scar on imaging. Elevated NT-Pro BNP and high-sensitivity Troponin T predict cardiovascular events(2) and a short term reduction in NT-pro BNP correlates with lower primary endpoints in phase 3 trials of heart failure.(3) Patient reported outcome questionnaires that may be used to support drug and device approval claims include the Kansas City Cardiomyopathy Questionnaire (KCCQ) and the Center for Epidemiologic Studies Depression Scale (CES-D) which correlated with overall quality of life in patients with acute myocarditis.(4)

Resolution of heart block is a clinically relevant endpoint that could serve as the primary end-point in a trial focused on treatment of the common clinical scenario of recent onset, sarcoidosis-related heart block. Key secondary endpoints in such a trial include patient reported (PRO) quality of life metrics with prespecified analyses of physical heath, depresion and health-related anxiety. VA burden can serve as both a secondary efficacy and safety endpoint in boith acute and more chronic populations with cardiac sarcoidosis. The burden of VA likely varies with time from start of immunosuppression and background antiarrhythmic and heart failure therapies.

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Cardiac Disease Assessment

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Cardiac MRI (CMR) is an established imaging modality used for the diagnosis of CS given its ability to provide a comprehensive assessment of both myocardial function and structure with detailed tissue characterization. (1) The functional assessment with parameters including ejection fraction, ventricular volumes, seems to be more accurate than any other modality in non-ischemic cardiomyopathies. (2) CMR techniques, such as late gadolinium enhancement (LGE), T1 and T2 mapping, and extracellular volume measurements, provide detailed evaluation of myocardial oedema/inflammation and fibrosis. LGE detection and extent has a pivotal role in the risk stratification of patients with CS. (3) As a result, international guidelines highlight the role of CMR in the management of sudden cardiac death in patients with CS. (4, 5)

To date CMR has been used as a secondary endpoint in two clinical trials in CS. (8, 9) Extent of LGE change was selected as secondary endpoint in both trials, while serial left ventricular ejection fraction focusing on cardiac function response and change in T2 mapping aiming to assess inflammatory response were used in MAGiK-ART and CHASM CS trials respectively. (8, 9)

Although the left ventricular dysfunction and extent of myocardial fibrosis detected by CMR have a strong prognostic value in CS, the role of CMR as endpoint in clinical trials remains controversial. The assessment of myocardial inflammation using CMR remains technically challenging and often limited by the presence of artefacts and significant inter-operator variability. (6) Furthermore, the reproducibility in detecting active inflammation has not been fully evaluated or standardized in clinical studies of cardiac sarcoidosis. T2 imaging can identify oedema, but measuring its extent and severity with precision remains complex. On the other hand, FDG-PET remains the modality of choice for the assessment of myocardial inflammation in CS with optimal quantification techniques. (7)

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WASOG Cardiac Sarcoidosis Trial Endpoints: Nuclear Medicine Endpoints:

David Birnie

Three potential endpoints were discussed:

- Myocardial Perfusion defect size ('scar score')
- Changes in cardiac FDG uptake
- Disease Remission (off Therapy)

The first two are surrogate endpoints; it is accepted that the validity of surrogate endpoints is assessed by the following criteria:

1. Biological plausibility
2. Observational studies showing a constant association between the surrogate and the endpoints of interest
3. Finding that the reduction of the surrogate also reduces the ultimate endpoints of interest
4. In addition, for rare diseases, to help with validation, extrapolation from other diseases is accepted

Myocardial Perfusion Defect Size

Myocardial perfusion imaging (MPI) is a nuclear medicine technique for quantifying myocardial scar. The scar score is variably called summed rest score (SRS), or perfusion defect (PD). We are using this endpoint as the primary in CHASM CS -1 RCT.It should be noted that there is some confusion in the CS literature about MPI. Strictly, MPI is a quite distinct test from FDG PET scanning (although it is performed simultaneously with FDG-PET scanning in many centers). We are using this endpoint as the primary in CHASM CS -1 RCT (1).

Criteria number	
1.	Extensive literature in multiple cardiomyopathies, showing that there is a dose response relationship between extent of myocardial scar and adverse clinical cardiac events.
2.	*1.Patel et al (2)* 97 patients, treatment naïve.

	LVEF, history of VT/VF and SRS were predictive, FDG uptake on PET was not. *2.Okafor et al (3)* 113 patients, treatment naïve. PD extent was the main significant predictor of outcome even after accounting for LVEF and change in SUVmean.
3.	38 patients (4) Myocardial perfusion reduction after steroid therapy was significantly associated with a low incidence of clinical events
4.	Multiple studies have shown that PD size has important prognostic value in coronary disease

Cardiac FDG uptake

Criteria number	
1.	The goal in treating active CS is to prevent fibrosis. The relationship between FDG uptake and fibrosis is far from consistent. Indeed, there may be a significant subset of cardiac sarcoidosis patients who never lay down fibrosis and probably do not need to be treated at all, analogous to pulmonary sarcoidosis.
2.	Modest quality data
3.	Modest quality data
4.	No data from other diseases to extrapolate from

Disease Remission (off Therapy)

The literature investigating disease remission (also known as disease termination) has major limitations, primarily because of variable definitions and hence the reported rates of remission vary widely. We have reported remission rates, assessed by serial FDG -PET imaging, of 33% and 92% after treatment with prednisone monotherapy and prednisone followed by 3 years of methotrexate, respectively (5). We likely will be using this endpoint as the primary in CHASM CS -2 RCT.

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