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

WASOG clinical trial endpoint task force: Executive summary

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Abstract. Over the past few years, an increased number of clinical trials have been performed evaluating specific therapies for pulmonary and cardiac sarcoidosis. However, a lack of consensus remains for appropriate clinical trial endpoints. In 2024, the World Association of Sarcoidosis and Other Granulomatous disease (WASOG) established a clinical trial endpoint Task Force to update the 2011 WASOG Task Force. This initiative was spearheaded by five sarcoidosis specialists (RPB, EEL, DAC, MAJ, AUW) and enlisted a total of 55 stakeholders, including 37 health care providers, 14 industry representatives, and 4 patients. In March 2025, 46 stakeholders participated in a one-day meeting which included twenty focused talks regarding clinical trial endpoints for pulmonary and cardiac sarcoidosis trials. A compilation of individual talk summaries was prepared and distributed to all stakeholders, including those unable to attend the meeting. Based on feedback from all stakeholders, the team leaders developed a series of statements reflecting the presentations and discussions with subsequent anonymous voting by all stakeholders. The majority of the voters endorsed thirteen specific clinical trial endpoint statements: two evaluating overall trial design, seven regarding pulmonary sarcoidosis, and four discussing cardiac sarcoidosis.

Key words: clinical trial, prednisone, spirometry, health-related quality of life

Introduction

In 2025, a task force was created by the World Association of Sarcoidosis and Other Granulomatous diseases (WASOG) to evaluate clinical trial endpoints in pulmonary and cardiac sarcoidosis. Despite a marked increase in sarcoidosis clinical trials, endpoints remain poorly defined and non-standardized. Since 2000, 15 placebo-controlled trials have been completed and analyzed using a variety of endpoints (1). Figure 1 lists the multiple endpoints evaluated in the 15 placebo-controlled treatment trials involving 769 pulmonary patients with the forced vital capacity (FVC) reported in 13 of 15 studies (1). In addition to the range of reported endpoints, the figure emphasizes the lack of one single endpoint being common to all investigations. Placebo-arm analysis from several of these trials revealed that FVC percent predicted changed by as much as 2% during the course of study (1). Currently ongoing or recently completed trials by aTyr (NCT05415137), Kinevant (NCT 05314517), and Xentria (NCT 05890729) are using steroid withdrawal, KSQ-Lung, and FVC % predicted as their primary and/or secondary endpoints. The results of these trials are not yet available, but they should prove useful in validating individual endpoints.

Two previous task forces, the WASOG Task Force 2011 (2) and Sarcoidosis Outcome Taskforce (SCOUT) (3) have evaluated candidate endpoints for pulmonary sarcoidosis trials. However,

Received: 2 September 2025
Accepted: 25 September 2025
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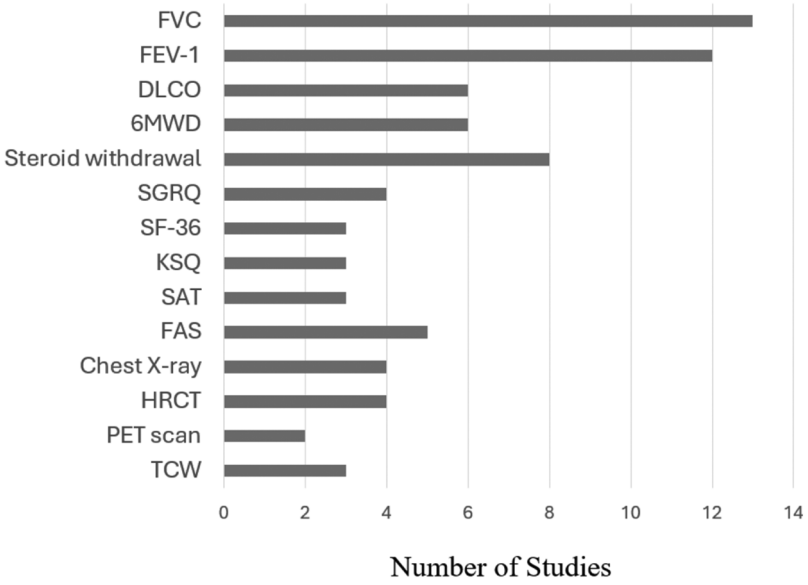

Figure 1. Clinical trial endpoints from 15 randomized trials including 769 pulmonary sarcoidosis patients. FVC: forced vital capacity, FEV-1: force expiratory volume in one second; DLCO: diffusion lung of carbon monoxide; 6MWD: six minute walk distance; SGRQ: Saint George Respiratory Questionnaire; SF-36: short form 36; KSQ: Kings Sarcoidosis Questionnaire; SAT: sarcoidosis assessment tool; FAS: fatigue assessment tool; HRCT: high resolution computer tomography scan; PET: positron emission tomography; TCW: time to clinical worsening. Updates from Baughman et al (1).

there remains little consensus regarding endpoints for clinical trials in sarcoidosis. The mission of the current Task Force is to update the status of clinical trial endpoints which can provide a pathway for future trial design incorporating the concept of patient feels, functions, and survives. This can be achieved with the development and approval of specific statements regarding clinical trial endpoints for patients with pulmonary or cardiac sarcoidosis.

Methods

The team leaders consisted of five sarcoidosis experts (RPB, DAC, MAJ, EEL, and AUW) who identified and invited international participants in clinical trials for pulmonary and cardiac sarcoidosis. Additional members included those with a dedicated interest in sarcoidosis from industry and global patient groups. Table 1 summarizes the features of the participating stakeholders with individual names provided in the Table 2.

The Team Leaders highlighted specific areas for Task Force discussion including patient recruitment, clinical trial endpoints from past and current studies, pulmonary sarcoidosis assessment and treatment changes for pulmonary disease, and cardiac disease. All speakers were provided with the results of a 2024 Delphi study performed by Drs Baughman, Grutters, and Lower which evaluated several domains of potential clinical trial endpoints for steroid dependent pulmonary sarcoidosis patients including trial design, pulmonary function testing, health related quality of life (HRQoL), steroid reduction, chest imaging, biomarkers, and composite endpoints (2). Using a threshold of $\geq$ 70% agreement, the Delphi panel achieved consensus for 38 of 97 statements. These statements were provided to the speakers and referenced throughout the meeting.

There were five areas led by individual team leaders: Sarcoidosis Clinical Trial Design (Lower); Corticosteroids (Culver); Pulmonary assessment (Judson), Assessing treatment response (Baughman); and Cardiac Disease (Wells). Twenty topics were covered by a didactic presentation followed by a discussion period (see Supplementary File 1 - online). To facilitate interaction and possible Task Force agreement, the discussion time slots included an automatic response system, Slido (https://www.slido.com/),

Table 1. Stakeholder Participants in WASOG Clinical Trial Endpoints Task Force

Total number of participants	55
Number on-site	46
Country of Origin	
Canada	1
France	3
Germany	1
India	1
Italy	4
Japan	1
Netherlands	4
Poland	1
Switzerland	1
Taiwan	1
United Kingdom	4
USA	33
Self-identified Status	
Health Care Provider	37
Industry	14
Patient	4

which allowed participants to provide live feedback. More than half of the Task Force meeting was devoted to discussion.

Within three weeks of the meeting, synopses were created by the individual speakers and edited by the respective Team Leader for each section. These summaries are provided in the meeting supplement (Supplement Compilation S2). These individual chapters were used to prepare this Executive Summary.

Subsequently, the Team Leaders, with additional feedback from stakeholders, developed a series of Task Force statements, which were distributed to all Task Force Stakeholders. Using the RedCAP system (2), forty-three (78%) of all Task Force Stakeholders voted on all 13 statements with voting options of agree, disagree, or no opinion. The percentage who agreed with individual statements was calculated for all voters. The results of the voting for all those who voted as well as for only those who had an opinion are shown in Table 3.

Summary of presentations

Sarcoidosis clinical trial design

Study design and analysis provide the backbone for successful clinical trials. Candidate endpoints must be pertinent for the intervention and population inclusion and exclusion criteria with the analysis predefined prior to study unblinding. The effect size, which establishes sample size, is based on precedence or extrapolated from feasible size. Because the term "clinically important difference" can be ambiguous, changes within an individual patient or between patient groups may be better captured using meaningful score difference. Furthermore, analysis should include data type (interval, categorical), distribution (parametric, non-parametric), and a process for handling outliers.

Close collaboration among investigators and their associations with patients, industry, and regulatory agencies can provide standardized diagnostic criteria, guide therapeutic trials, identify research gaps, and enhance networks. Definition of a "clinically meaningful" endpoint may differ for a regulatory agency versus representatives of clinical care or industry. Without a regulatory precedent, efficacy endpoints need to directly assess "feels, functions, and survives", or be validated surrogates. Industry sponsors should determine the unmet needs along with symptoms, testing, or markers that support intervention efficacy benefit. In addition to achieving a trial endpoint, payers are likely to require data on clinical utility such as lung function testing, steroid reduction, HRQoL, or radiographic improvements.

Understanding the pitfalls encountered in previous successful clinical trials can enhance the likelihood of future success. For instance, the EFZO-Fit trial of 268 randomized patients from 10 countries is the largest treatment study in pulmonary sarcoidosis. Although this clinical trial exceeded target enrollment of 264 patients, it encountered challenges in site selection, patient recruitment, and protocol design. Enrollment criteria necessitated high screened numbers, and the protocol required experienced principal investigators. These challenges resulted in the activation of only 104 of 315 feasibility sites, with 19 sites enrolling no patients, and 85 sites (82%) enrolling at least one patient. The bulk of patients were recruited from internal databases. This experience emphasizes that a better initial understanding of the

Table 2. WASOG Task Force Participants

Name		Country	Status
Robert	Ashworth	USA	Industry
Arata	Azuna	Japan	HCP
Matthew Charles	Baker	USA	HCP
Elena	Bargagli †	Italy	HCP
Robert	Baughman *§	USA	HCP
John	Belpeiro	USA	HCP
David	Birnie *	Canada	HCP
Surinder	Birring *	United Kingdom	HCP
Francesco	Bonella *	Germany	HCP
Catherine	Bonham	USA	HCP
Lisa	Carey *	USA	Industry
Leslie	Cooper *	USA	HCP
Elliott	Crouser *	USA	HCP
Dan	Culver *§	USA	HCP
Sujal	Desai *	United Kingdom	HCP
Wonder	Drake †	USA	HCP
Alicia	Gerke	USA	HCP
Shawn	Grant	USA	Industry
Jan	Grutters *	Netherlands	HCP
Rohit	Gupta	USA	HCP
Logan	Harper *	USA	HCP
Kerry	Hena †	USA	HCP
Kerry	Hena †	USA	HCP
Tom	Hoggan	USA	Industry
Dominique	Israel-Biet	France	HCP
Piotr	Iwanowski	Poland	Industry
Florence	Jeny *	France	HCP
Marc	Judson *§	USA	HCP
Vivinne	Kahlmann *	Netherlands	HCP
Vasilis	Kouranos †	United Kingdom	HCP
Elyse	Lower *§	USA	HCP
Fillipo	Martone *	Italy	Patient
Carie	Masoner	USA	Industry
Tom	Matthews	USA	Industry
Adam	Morgenthau †	USA	HCP
Vis	Niranjan	USA	Industry
Ogi	Obi *	USA	HCP

Name		Country	Status
Antje	Prasse †	Switzerland	HCP
Sujeet	Rajan †	India	HCP
Ted	Reiss †	USA	Industry
Michelle	Sharp *	USA	HCP
Sanjay	Shukla	USA	Industry
Noopur	Singh *	USA	Industry
Paolo	Spagnola †	Italy	HCP
Peter	Sporn	USA	HCP
John	Stone *	USA	HCP
Eileen	Sun	USA	Industry
Nadera	Sweiss	USA	HCP
Dominique	Valeyre †	France	HCP
Bernt	van den Blink	USA	Industry
Marcel	Veltkamp *	Netherlands	HCP
Athol	Wells *§	United Kingdom	HCP
Marlies	Wijsenbeek	Netherlands	HCP
Andrea	Wilson *†	USA	Patient
Wenjiin	Yang †	Taiwan	Industry
Gianluca	Ziosi	Italy	Patient

*Speaker; §Team Leader; †Not present at March 8, 2025 meeting.

study protocol and patient population can improve patient recruitment and enrollment rates.

It is essential that all clinical trial endpoints be patient focused and relevant. Patient surveys suggest that HRQoL and functionality are the highest patient priorities (3). The Sarcoidosis Patient Advisory Group (SPAG) of the European Lung Foundation (ELF) stresses awareness among patients, caregivers, health care providers, policy makers, and the public. The SPAG encourages scientific societies to facilitate timely diagnosis, multidisciplinary care, and recognition of referral centers. Furthermore, the group highlights the unmet needs of effective pain management, psychological support, fatigue and sleep evaluation, and prevention of secondary damage from corticosteroids.

In conclusion, the clinical trial landscape consists of organized, global patient voices that are closely engaged with investigators who desire collaboration with industry, regulatory agencies, and payors. However, future goals stress the importance of better validated, clinically relevant trial endpoints and further exploration of possible interactions among unidimensional variables such as pulmonary physiology and symptoms.

Corticosteroids

Oral corticosteroids (OCS) are widely used today, despite increasing awareness of their short- and long-term toxicity profiles (4). They have maintained a position in the overall treatment landscape as "first-line" for several reasons: familiarity, ease of use, accessibility, cost, effectiveness, speed of onset, perceived cumbersomeness and toxicity of steroid-sparing alternatives, and a dearth of rigorous clinical studies supporting the benefits of other medications. The available literature suggests that in the short-term OCS are effective for pulmonary sarcoidosis to improve chest radiographic findings, FVC, and DLCO (5, 6). Historically dosing regimens have likely been too high, as a starting dose of prednisone 20 mg/d

Table 3. WASOG Task Force Endorsed Statements

1. Clinical trial endpoints should be designed by a team of clinical researchers, patients, and industry representatives. The selection of individual endpoints should be driven by feasibility, safety, sample size consideration, usefulness for regulatory approval and ability to recruit patients.
2. For studies seeking regulatory approval, clinical researchers, patients, and industry representatives need to provide input at the time of study application.
3. Clinical trial endpoints to be considered for steroid-dependent pulmonary sarcoidosis patients include Forced Vital Capacity (FVC), Kings Sarcoidosis Questionnaire (KSQ), and prednisone reduction.
4. For use as a unique clinical trial endpoint, changes in FVC or KSQ should be analyzed as a continuous variable.
5. For use as a unique clinical trial endpoint, change in prednisone dosage should be analyzed as a continuous variable.
6. For use as a unique clinical endpoint, prednisone reduction should include the proportion of patients achieving total discontinuation or reduction to a daily prednisone dose of 5 mg or less.
7. For use of prednisone reduction as a unique clinical trial endpoint, decisions on re-escalation should include clinical judgement.
8. For use as a unique clinical trial endpoint, time to clinical worsening should include sarcoidosis related hospitalization, death, or transplantation, or increase in prednisone dose for sarcoidosis for more than two weeks or 10% or greater decrease in FVC% predicted or an eight-point or greater decrease in KSQ-Lung scale on two consecutive measurements.
9. When comparing two treatment outcome arms, the definition of non-inferiority includes 5% or less change in FVC percent predicted or an 8-point or less change in KSQ-Lung scale.
10. In most cardiac sarcoidosis trials, no single endpoint is a suitable primary endpoint for all trials due to variations in trial populations and goals.
11. In most cardiac sarcoidosis trials, if an advanced imaging endpoint is selected as a primary endpoint, a clinical secondary endpoint should be included, both to broaden the evaluation of efficacy and to identify unexpected deleterious clinical effects.
12. In most cardiac sarcoidosis trials, PET is the preferred advanced imaging modality with choice of PET variable dependent on trial context (i.e. change in inflammatory signal versus change in fibrosis as judged by myocardial perfusion imaging).
13. For use as a unique clinical trial endpoint in cardiac sarcoidosis trials, changes in PET signal should be analyzed as a continuous variable.

appears to be equivalent to higher doses (7). Furthermore, the maximum OCS benefit is usually seen within 4 weeks. For chronic sarcoidosis, between 20-80% of patients relapse following OCS cessation (8, 9), implying that a decision to start therapy often portends a need for a less toxic strategy for long-term therapy (10). As a result of increasing awareness of steroid toxicity and the need to shift the treatment paradigm to other agents, WASOG has developed a Steroid Stewardship document (submitted).

An international survey of 1911 patients from 34 countries suggested after propensity matching that those patients who had ever received OCS for sarcoidosis experienced higher odds (range 1.9-3.8) for a range of toxicities, including diabetes, hyperlipidemia, osteoporosis, and infections (oral communication, Logan Harper, MD). The median weight gain among ever-users was 7.5 kg, with one in eight individuals gaining more than 20 kg. None of these toxicities was substantially different when current users were compared to ever-users, suggesting that initiating OCS, regardless of plans to taper, may lead to irreversible chronic comorbidities in many patients.

Reduction of corticosteroid exposure during a clinical trial can be quantified using tools like the Glucocorticoid Toxicity Index (GTI) (11). The GTI is a brief instrument comprised of common, dynamic, and relevant variables that are mostly accessible during routine clinical care. It has been successful in substantiating the benefits of reducing glucocorticoid exposure in clinical trials and supporting regulatory applications for medication approval (12, 13). Since GTI changes may be evident within 13 weeks (12), implementing the GTI is feasible in Phase 2 and 3 trials. While the use of GTI in assessing glucocorticoid toxicity has not been specifically incorporated in sarcoidosis clinical trials to date, the committee was strongly supportive of adding GTI as an important toxicity endpoint. One issue is the sensitivity of the GTI in detecting toxicity in sarcoidosis trials, where the average dose of prednisone is lower than that in vasculitis trials, where GTI has been effective

in identifying changes in glucocorticoid toxicity with different treatment regimens (12).

Although OCS reduction has been used as a clinical trial endpoint (14, 15), currently randomized controlled trials have not rigorously evaluated the effects of steroid reduction on comorbid conditions. In the recently completed Delphi study, consensus was obtained for the use of steroid sparing effects as key trial endpoints. Although three OCS reduction endpoints received endorsement, the Delphi experts favored the endpoints of either an absolute reduction of prednisone to ≤ 5 mg/d or a relative reduction by 50% from baseline OCS dose over total OCS cessation. The overall sentiment of the Task Force participants was that the steroid sparing effect is a key trial design strategy and a valuable endpoint for clinical trials in the steroid dependent sarcoidosis population either as an end itself or as a means to achieve reductions in measured OCS toxicities. The Task Force formed consensus on the proposition that the proportion of patients who had reduced prednisone dose to 5 mg or less or who had discontinued prednisone altogether were important endpoints.

Pulmonary assessment

The primary rationale for the use of anti-inflammatory therapy in pulmonary sarcoidosis is to improve function in order to improve quality of life. Therefore, pulmonary physiological endpoints are reasonable in pulmonary sarcoidosis trials. Pulmonary sarcoidosis patients with normal pulmonary function are often excluded from consideration in such trials because of concern that little capacity exists for further physiological improvement with therapy. However, individual patients may improve with treatment. This includes those with significant symptoms and normal population-based pulmonary function parameters but an individual decline in pulmonary function compared to their premorbid baseline Additionally, those patients with pulmonary sarcoidosis who have severe pulmonary dysfunction may be excluded from clinical trials because of a concern that fibrosis is unlikely to respond to anti-inflammatory therapy (14, 16); however, such patients often have co-existing active granulomatous inflammation that may respond to treatment (17, 18).

Spirometry, specifically the FVC, has been the preferred endpoint for pulmonary sarcoidosis trials (19). However, the primary physiological abnormality in a large percentage of pulmonary sarcoidosis patients may be an obstructive ventilatory defect (20, 21). Although the DLCO may identify pulmonary disorders that are undetected by other pulmonary function tests (e.g., pulmonary hypertension (22)) the extreme intersession variability in the DLCO makes it a problematic trial endpoint choice.

Because HRQoL is a major indication for sarcoidosis treatment (12) and of primary concern to patients (13), this parameter could be considered as a primary or a key secondary clinical trial endpoint. At a minimum, HRQoL symptoms and physical functioning should be measured in clinical trials to document therapeutic impact and ensure there is no significant worsening with treatment. Both HRQoL and pulmonary symptoms have been used as endpoints in numerous sarcoidosis trials, and several assessment tools are sarcoidosis-specific with established minimally clinical important differences (MCIDs) (23). However, these studies are not to regulatory standards.

Chest imaging, specifically HRCT, may be an endpoint in pulmonary sarcoidosis trials as it can detect anatomic features of granulomatous inflammation and pulmonary fibrosis. Although HRCT imaging phenotypes of pulmonary sarcoidosis have recently been described (24), using them as clinical trial endpoints may be hampered due to lack of validation and intra- and inter-observer variability. Advances in artificial intelligence (AI) and machine learning (ML) may provide rigorous and standardized image interpretation that may reduce observer variability and provide testable quantitative chest imaging endpoints (24, 25). By incorporating unsupervised AI/ML, this process may aid in unraveling HRCT and PET features that are "hidden" to the human eye (24).

Only five to nine percent of sarcoidosis patients die from their disease (26), and when death from sarcoidosis does occur, it is often decades after disease onset (27). These factors illustrate why mortality from sarcoidosis remains problematic as a primary endpoint in pulmonary sarcoidosis trials. Certain subgroups of pulmonary sarcoidosis patients, including those with significant pulmonary fibrosis (19), pulmonary hypertension (20), and sarcoidosis-related hospitalization (21), have higher mortality rates than unselected cohorts. The annualized mortality rates in these subgroups are too low to use as clinical trial primary endpoints. However, it is reasonable to

include mortality as part of a composite primary trial endpoint in combination with other events indicative of clinical worsening.

How to assess treatment response

When evaluating individual parameters, such as the FVC, it is important to determine if cohort change or individual patient change is being assessed for treatment response. For the individual patient, change is very likely true if it is at least 1.64 times the coefficient of variation (28). In one study of 18,000 adult patients, the 90th percentile reproducibility estimates for individual patients within session are as high as 5.3% and 150 ml. For group distributions of the FVC percent predicted, the reproducibility of FVC percent predicted is 2.6% and the standard deviation is 2.9% (29).

The most commonly reported pulmonary function parameter, FVC, can be reported as change in absolute volume or as change in the percent predicted value. Many experts suggest that the change in both should be reported, but the FVC percent predicted has been the most commonly reported variable (30). In a recent Delphi survey, sixty percent of sarcoidosis clinical trial experts concluded that changes in FVC should be analyzed as percent predicted rather than absolute volume. In that same Delphi, the experts considered FVC clinically meaningful when the within change in FVC percent predicted was 10% or greater. It should be noted that values for 5-10 percent were not queried. Unfortunately, published studies of effective anti-sarcoidosis medications have reported much smaller FVC changes (16, 31-34). Alternatively, more relevant data may be collected by analyzing the change in FVC as a continuous variable. Although using categorical values may ease interpretation, this arbitrary cut-point may result in loss of information, reduction in power, and increase both type I and type II errors (28, 35, 36). Over three quarters of the WASOG Task Force stakeholders felt that FVC should be analyzed as a continuous rather than a categorical variable.

The Delphi survey experts ranked HRQoL as the most important endpoint in clinical trials and the Kings Sarcoidosis Questionnaire (KSQ) (37) as the most popular instrument. While the MCID for KSQ Lung of 4 points has been reported (38), there is significant variability on repeated KSQ testing, especially for those with mild (KSQ>70) or severe (KSQ<40) symptoms (39). Due to insufficient validation, patient reported outcomes (PROs) are currently not considered valid by regulatory agencies as primary endpoints for a Phase 3 clinical trial. However, PRO validation can occur with further qualitative investigation regarding concept elicitation and cognitive debriefing along with the identification of clinically important thresholds using Phase 2/3 prospective intervention and placebo trial data. This would include responder analysis (40).

Of the three major chest imaging modalities queried in the Delphi study, (chest x-ray, HRCT, and PET), only PET scanning achieved consensus for use as a clinical trial endpoint for pulmonary sarcoidosis. Likely, this reflects its current use as a trial endpoint in several randomized, placebo-controlled trials. To date, the results are incompletely reported; but based on current information, the Task Force members considered PET scanning for pulmonary sarcoidosis only useful as a proof of concept or supportive tool for other parameters (41). In addition, the test is expensive and associated with considerable radiation exposure. The discussants at the Task Force felt that other imaging modalities, especially HRCT, can be relevant endpoints if further validation is performed.

Consensus was achieved by the Delphi experts for prednisone withdrawal as a clinical trial endpoint. In an analysis of multiple clinical trials, half of placebo-treated patients experienced prednisone reduction; however, only ten percent of patients were able to discontinue OCS completely (1). Task Force members also felt that when steroid re-escalation is desired, clinical judgment is preferable to rigid or pre-determined thresholds (e.g. change in FVC). Additional Delphi consensus was achieved for several other proposed trial endpoints, including the need for a 3-month follow-up after planned prednisone withdrawal because delayed relapse may not be identified for 3-6 months after prednisone discontinuation (42).

The change in prednisone dose as a clinical trial endpoint can be reported in various ways. Analysing the change in prednisone dosage as a continuous variable avoids the study power cost of dichotomizing continuous variables (36). There was general consensus that any reduction in OCS dose change is meaningful.

The concept of a composite endpoint was appealing. The group felt a composite endpoint should

include steroid withdrawal, pulmonary function, and HRQoL. Relapse with steroid withdrawal was proposed as one composite endpoint. The group focused on the use of time to clinical worsening (TCW) as a composite endpoint. TCW is a well-established primary clinical trial endpoint in many progressive conditions, including malignancy, sarcoidosis associated pulmonary hypertension (43), and progressive pulmonary fibrosis in sarcoidosis (44). Disease-associated death is an accepted component of most TCW endpoints. However, since death due to sarcoidosis rarely occurs in the context of a clinical trial, it is not useful as an endpoint by itself. On the other hand, disease-associated hospitalization and time to relapse, as defined by need for an increase of therapy, are important parameters to be considered for inclusion. For the Delphi stakeholders, there was also consensus that an FVC% predicted decline of at least 10% or a KSQ-lung decrease of at least 8 points should be included as criteria for TCW. However, these two cut-offs were not based on rigorous studies but reflect expert opinion. While MIDs for KSQ Lung and GH have been calculated from a large prospective study (38), that study did not include a standard treatment regimen. Future studies with standardized therapy and evaluation may provide support for these or other cut-off values.

Task Force members agreed that when comparing two groups, either with different initial therapy such as in the PREDMETH study (45), or after prednisone withdrawal, treatment outcomes could be evaluated with equivalence. Additionally, it was agreed that a significant prednisone reduction could be considered meaningful if there was a non-inferior difference between groups, such as a FVC % predicted difference of 5% or less and/or a KSQ-lung change difference of 8 points or less. We are aware of few non-inferiority studies in sarcoidosis. There are several challenges in designing non-inferiority studies. In infectious disease, cardiovascular disease, and oncology trials, the non-inferiority concept has been widely used. Recent analysis of these studies emphasizes the limitations of non-inferiority study design and emphasizes the importance of superiority trials (46-48). Non-inferiority trials need to have a well-defined endpoint, assurance that the comparator therapy is effective (usually FDA approved), and that blinding is maintained for patient and treating health care provider. For treatment of steroid-dependent pulmonary sarcoidosis patients, the variability of FVC and KSQ-lung led to only a conditional acceptance of FVC % predicted difference of 5% or less and/or a KSQ-lung change difference of 8 points or less. Future studies may help solidify these cut-off values.

Cardiac sarcoidosis

Few clinical trials have been performed in cardiac sarcoidosis, with the ongoing CHASM trial the first prospective randomized controlled trial (49). Based on current data, it is not possible to specify any single primary or key secondary endpoint for all trials. This reflects the varying goals of treatment trials including proof of concept trials in small patient cohorts, as well as studies addressing individual clinical problems (such as heart block and ventricular arrhythmias [VA]) and cardiac disease activity. End-point selection may be influenced by whether trial design is that of non-inferiority, comparing two regimens, or superiority against placebo or current routine therapies. Finally, trials of novel agents in treated patients may be compared to withdrawal of existing therapy, especially OCS. Despite these constraints, broad principles of end-point selection can be constructed.

The selection of solitary clinical endpoints is driven by trial context. For example, a trial examining the reversal of heart block might logically have heart-block reversal as a primary endpoint. Important clinical end-points might include PROs, HRQoL metrics (50), and VA burden, as these endpoints are equally relevant in acute and chronic cardiac sarcoidosis. Mortality and other hard clinical endpoints (e.g. heart failure associated hospitalization) are not suitable as solitary clinical endpoints, as they are infrequent.

Regarding imaging variables, the Task Force agreed that preferred modalities measure scar plus or minus inflammatory burden. Although widely available and relatively inexpensive, echocardiography is not sensitive in detecting scar (51). Cardiac magnetic resonance (CMR) is the gold standard tool for imaging myocardial scar in multiple cardiac diseases; however, implanted devices may interfere with CMR image quality. Since many sarcoidosis patients have implanted devices, this can be a study limitation. While MRI compatible devices are available, cardiac specific MRI may not be readily available, and it is prone to shadowing artefact (52). Also, CMR is less sensitive than cardiac FDG-PET imaging for

reliably quantifying inflammation (53, 54). Cardiac FDG-PET scanning provides sensitive information on changes in inflammatory signal, and simultaneous myocardial perfusion imaging can provide information about changes in fibrosis driven by inflammation (49, 55). Thus, cardiac FDG-PET with or without perfusion imaging is currently the preferred imaging modality as a primary endpoint or a key secondary endpoint. However, the choice of FDG-PET scanning vs CMR as most appropriate may depend on trial context. FDG-PET may be best for proof of concept in early phase trials that seek to demonstrate anti-inflammatory effects. In advanced phase trials, CMR may be preferred to document changes in cardiac fibrosis as a consequence of inhibiting inflammation.

While imaging changes remain the primary focus of therapeutic trials, outcome information including changes in ejection fraction, VA burden, and major adverse cardiac events (MACE) should also be collected to ensure that no therapy is associated with an increased risk of untoward events.

As a general principle, the Task Force members suggest that in most cardiac sarcoidosis trials, a clinical or advanced imaging endpoint may be selected as a primary endpoint with a key secondary endpoint chosen from the other domain. However, the choice of a primary endpoint and a key secondary endpoint is critically dependent on trial goal and study design.

Future areas of potential importance

A recent study in pulmonary sarcoidosis patients found that impedance oscillometry measurements correlated more strongly with HRQoL measures than spirometry and other traditional pulmonary function measurements (56). In addition, impedance oscillometry detected airflow obstruction in more than 50% of patients (57) which is greater than the rates detected by spirometry (58, 59). Including impedance oscillometry as an exploratory endpoint in clinical trial could provide information of its performance as an endpoint (60).

Given the interest in HRQoL as a clinical trial endpoint, the Task Force supported the need to perform more studies validating HRQoL instruments. For example, studies determining meaningful response scores of KSQ and other outcome measures, should be performed by comparing them against various clinical and other HRQoL anchors. This is especially important in placebo-controlled trials.

Cough is an important complaint for sarcoidosis patients (61). Some clinical trials have assessed the impact of therapy on cough (45, 62, 63). However, these studies relied on PROs, which have their limitations. Objective cough counting has been used in the cough field for years (64, 65), but is less studied in in sarcoidosis (66).

WASOG task force conclusions

As a result of the Task Force deliberations, the Team Leaders proposed 13 specific statements, which were subsequently distributed to all Task Force participants for comments and voting. A total of 43 Task Force participants completed the survey: health care providers (31), industry (8), and patients (4). For 11 of 13 statements, between one and twelve of 43 voters had "no opinion". Figure 2 shows the number of abstainers for individual statements. As noted, in some statements a significant proportion of voters abstained. This limitation may reflect insufficient current information or participant lack of knowledge regarding a specialized topic. It may also reflect a disagreement with the premise outlined in the question stem, or uncertainty about its applicability in diverse trial scenarios.

The stakeholders approved all 13 statements (Table 3). Table 4 shows the calculated percentage of all voters and the percentage excluding the abstainers for each statement. Excluding abstainers, twelve of the statements had strong support (more than 70% approval), with only Statement 10 having only 69% approval. While some specific tests were identified as potential end points, the Task Force recognized that other end points could be useful. However, in the absence of data, no additional specific conclusions were generated. For pulmonary trials, the Task Force members' comments were focused on steroid-dependent patients; however, the statements may be applicable for other trial designs. Figure 3 is a summary of the various clinical trial endpoints discussed for pulmonary trials, with suggested placement as primary, secondary, or exploratory endpoints based on current evidence.

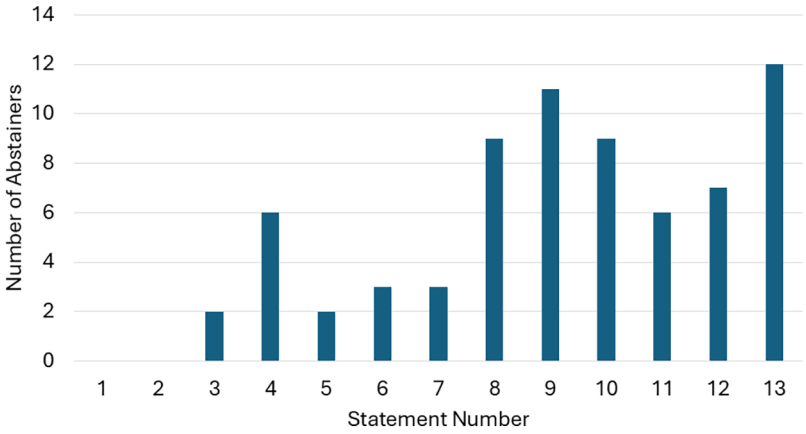

Figure 2. The number of Task Force participants who abstained from individual statements.

Table 4. Results of voting on individual statements: All voters and those with opinions

	All votes number	Yes positive	% positive	With an Opinion voters	Abstainers	Number with an opinion	% positive
1. Clinical trial endpoints should be designed by a team of clinical researchers, patients, and industry representatives. The selection of individual endpoints should be driven by feasibility, safety, sample size consideration, usefulness for regulatory approval and ability to recruit patients.	43	41	95.3%	43	0	41	95.3%
2. For studies seeking regulatory approval, clinical researchers, patients, and industry representatives need to provide input at the time of study application.	43	38	88.4%	43	0	38	88.4%
3. Clinical trial endpoints to be considered for steroid-dependent pulmonary sarcoidosis patients include Forced Vital Capacity (FVC), Kings Sarcoidosis Questionnaire (KSQ), and prednisone reduction.	43	37	86.0%	41	2	37	90.2%
4. For use as a unique clinical trial endpoint, changes in FVC or KSQ should be analyzed as a continuous variable.	43	33	76.7%	37	6	33	89.2%
5. For use as a unique clinical trial endpoint, change in prednisone dosage should be analyzed as a continuous variable.	43	37	86.0%	41	2	37	90.2%

Table 1 (*Continued*)

	All votes number	Yes positive	% positive	With an Opinion voters	Abstainers	Number with an opinion	% positive
6. For use as a unique clinical endpoint, prednisone reduction should include the proportion of patients achieving total discontinuation or reduction to a daily prednisone dose of 5 mg or less.	43	35	81.4%	40	3	35	87.5%
7. For use of prednisone reduction as a unique clinical trial endpoint, decisions on re-escalation should include clinical judgement.	43	38	88.4%	40	3	38	95.0%
8. For use as a unique clinical trial endpoint, time to clinical worsening should include sarcoidosis related hospitalization, death, or transplantation, or increase in prednisone dose for sarcoidosis for more than two weeks or 10% or greater decrease in FVC% predicted or an eight-point or greater decrease in KSQ-Lung scale on two consecutive measurements.	43	28	65.1%	34	9	28	82.4%
9. When comparing two treatment outcome arms, the definition of non-inferiority includes 5% or less change in FVC percent predicted or an 8-point or less change in KSQ-Lung scale.	43	22	51.2%	32	11	22	68.8%
10. In most cardiac sarcoidosis trials, no single endpoint is a suitable primary endpoint for all trials due to variations in trial populations and goals.	43	33	76.7%	34	9	33	97.1%
11. In most cardiac sarcoidosis trials, if an advanced imaging endpoint is selected as a primary endpoint, a clinical secondary endpoint should be included, both to broaden the evaluation of efficacy and to identify unexpected deleterious clinical effects.	43	36	83.7%	37	6	36	97.3%
12. In most cardiac sarcoidosis trials, PET is the preferred advanced imaging modality with choice of PET variable dependent on trial context (i.e. change in inflammatory signal versus change in fibrosis as judged by myocardial perfusion imaging).	43	36	83.7%	36	7	36	100.0%

	All votes number	Yes positive	% positive	With an Opinion voters	Abstainers	Number with an opinion	% positive
13. For use as a unique clinical trial endpoint in cardiac sarcoidosis trials, changes in PET signal should be analyzed as a continuous variable.	43	29	67.4%	31	12	29	93.5%

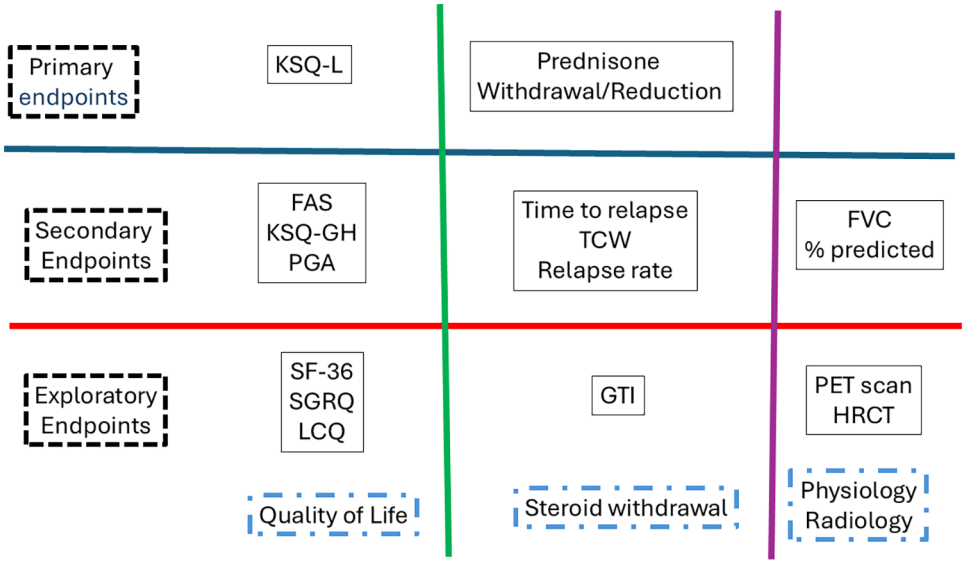

Figure 3. Based on currently available literature, a schematic proposal of the various clinical trial endpoints for pulmonary sarcoidosis, including those considered potential primary endpoints, secondary endpoints, and exploratory endpoints. KSQ-L: Kings Sarcoidosis Questionnaire-Lung; FAS: Fatigue Assessment Scale; KSG-GH: Kings Sarcoidosis Questionnaire- General Health; PGA: Patient Global Assessment; TCW: Time to Clinical Worsening; FVC: Forced Vital Capacity; SF-36: Short Form-36; SGRQ: Saint George Respiratory Questionnaire; LCQ: Leicester Cough Questionnaire; GTI: Glucocorticoid Toxicity Index; PET: Positron Emission Tomography; HRCT: High Resolution Computer Tomography.

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Appendix

Supplementary files

Supplementary File S1. See online