A feasibility study for a trial investigating the treatment of sarcoidosis-associated fatigue with methylphenidate

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Thesis abstract

Objectives - The research objective was to determine the feasibility of performing an appropriately-powered study investigating the use of methylphenidate for sarcoidosis-associated fatigue.

Methods - The *Fatigue and Sarcoidosis – Treatment with Methylphendiate (FaST-MP)* feasibility study was undertaken to compare methylphenidate with an identical placebo in a double-blind, randomised, parallel-arm study. Participants had the opportunity to discuss their perspectives on the study in post-trial focus groups.

Alongside *FaST-MP*, further work was undertaken to determine future study design. Activity monitors were piloted to determine the preferred device in patients with sarcoidosis. Quality of life measures were compared using data from a cohort of patients with sarcoidosis to understand the relationship between clinical outcomes.

Findings – Participant recruitment to the *FaST-MP* study was lower than expected (22 participants) but retention was high (100%) and the medication appeared well-tolerated and safe. No statistical difference in change in fatigue scores was seen between the methylphenidate and placebo arms, although both groups showed improvement from baseline fatigue scores. Participants reported a positive experience of the trial from focus group discussion but raised concerns relating to the fatigue outcomes used and the frequency with which fatigue was measured.

Comparison of quality of life questionnaires identified differences between two commonly used measures which may influence questionnaire choice in future studies investigating sarcoidosis-associated fatigue.

Conclusion - Designing a full phase III study to investigate the clinical efficacy of methylphenidate for sarcoidosis-associated fatigue appears feasible, although future study design must consider how to best reflect “usual care”, as well as the optimal outcome measures within such a study.

Table of Contents

List of Tables

List of Figures

Dedication

For Sarah and Cameron

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List of abbreviations

6MWT	Six-minute walk test
ADHD	Attention Deficit Hyperactivity Disorder
AE	Adverse Event
AHI	Apnoea-Hypopnoea Index
ALT	Alanine Transaminase
APC	Antigen presenting cells
AR	Adverse Reaction
ATS	American Thoracic Society
BMI	Body Mass Index
BP	Blood Pressure
CD4	Cluster of differentiation 4
CFS	Chronic fatigue syndrome
CI	Chief Investigator
CIS	Checklist Individual Strength
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CPET	Cardiopulmonary exercise test
CRDQ	Chronic respiratory disease questionnaire
CRP	C-reactive Protein
CT	Computed Tomography
CTA	Clinical Trials Authority
CTCAE	Common Technology Criteria for Adverse Events
CXR	Chest X-rays
D_LCO	Diffusing capacity of the lungs for Carbon Monoxide
DMEC	Data Monitoring and Ethics Committee
EBUS	Endobronchial ultrasound
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rates
EN	Erythema Nodosum
ENMO	Euclidean Norm Minus One-g
EQ-VAS	EuroQoL Visual Analogue Scale
EQ5D	EuroQoL-5 dimension-5 level questionnaire
ERS	European Respiratory Society
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy – Fatigue
FaST-MP	Fatigue and Sarcoidosis – Treatment with Methylphenidate (Feasibility study title)
FAS	Fatigue Assessment Scale
FDG	Fluoro-2-deoxy-D-glucose

FEV_1	Forced Expiratory Volume in 1 second
FSS	Fatigue Severity Scale
FVC	Forced Vital Capacity
GHS	General Health Status
GP	General Practice
GPS	Global Positioning System
HADS	Hospital Anxiety and Depression Score
HIV	Human Immunodeficiency Virus
HLA	Human leukocyte antigen
HR	Heart Rate
HRA	Health Research Authority
HRQoL	Health-related Quality of Life
ICD	International classification of diseases
IL	Interleukin
ILD	Interstitial Lung Diseases
IMP	Investigational Medicinal Product
IPAQ-SF	International Physical Activity Questionnaire – Short Form
IPF	Idiopathic Pulmonary Fibrosis
ITT	Intention to Treat
KCO	Transfer co-efficient of Carbon Monoxide
KSQ	Kings Sarcoidosis Questionnaire
L5	Mean accelerometer output during least active 5 hours
M5	Mean accelerometer output during most active 5 hours
MCID	Minimal Clinically Important Difference
MDT	Multidisciplinary Team
MeSH	Medical Subject Headings
MFI	Multifactorial disease inventory
MHC	Major histocompatability complex
MHRA	Medicines and Healthcare Products Regulatory Agency
mKatG	Mycobacterial catalase G
MMF	Mycophenolate Mofetil
mmHg	Millimetres of Mercury
MRI	Magnetic resonance imaging
MSWT	Modified Shuttle Walk Test
MVPA	Moderate or Vigorous Physical Activity
$MVPA_{10}$	Moderate or Vigorous Physical Activity using 10-minute bout criteria
NCTU	Norwich Clinical Trials Unit
NHANES	National Health and Nutrition Examination Survey
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
NIH	National Institute of Health

NIHR	National Institute of Health Research
NNUH	Norfolk and Norwich University Hospital
OSA	Obstructive sleep apnoea
PET	Positron emission tomography
PIC	Participant Identification Centre
PIS	Participant Information Sheet
PLMS	Periodic limb movement syndrome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analysis
PROSPERO	International Prospective Register of Systematic Reviews
PSQI	Pittsburgh Sleep Quality Index
QALY	Quality Adjusted Life Year
RCI	Repository Corticotropin
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
REDCap	Research Electronic Data Capture
SAA	Serum amyloid A
sACE	Serum Angiotensin Converting Enzyme
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SC	Safety Committee
SD	Standard Deviation
SF-12	Short form-12 item
SF-36	Short form-36 item
SF-6D	Short form-6 dimensions
SG	Standard Gamble
SmPC	Summary of Product Characteristics
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
SRT	Steep ramp test
SSRI	Selective Serotonin Reuptake Inhibitor
SUSAR	Suspected Unexpected Serious Adverse Reaction
T4	Thyroxine
TBLB	Transbronchial lung biopsy
TBNA	Transbronchial needle aspirate
T_H1	Type 1 helper T-cell
T_H17	Type 17 helper T-cell
TNF	Tumour necrosis factor
TSC	Trial Steering Committee
TSH	Thyroid Stimulating Hormone
TTO	Time Trade Off
UAR	Unexpected Adverse Reaction
UK	United Kingdom

USA	United States of America
VAS	Visual Analogue Scale
WASOG	World Association of Sarcoidosis and Other Granulomatous diseases
WHO	World Health Organisation
WHOQOL-100	World Health Organisation Quality of Life Scale – 100
WHOQOL-BREF	World Health Organisation Quality of Life Scale – Brief

Acknowledgement of specific contributions

Name	Position	Contribution
Dr Allan Clark	Senior Lecturer in Medical Statistics, Norwich Medical School	Input into the statistical design of the *FaST-MP* study (chapter 4), author of statistical analysis plan for *FaST-MP*, development of the randomisation schedule for *FaST-MP*, critical review of the dataset and analysis of *FaST-MP* (chapter 5), critical review of chapters 4 and 5.
Professor Ann Marie Swart	Director of Norich Clinical Trials Unit (NCTU)	Assistance with *FaST-MP* trial design, oversight of aligning *FaST-MP* with NCTU clinical trial practices.
Matthew Hammond	Senior Trials Manager, NCTU	Advice and development of trial specific working practice documents for *FaST-MP*, including quality management, safety practices and monitoring. Auditing of trial master file and leading monitoring visits for *FaST-MP* according to pre-specified schedules. NCTU representative on *FaST-MP* steering committee.
Dr Erika Sims	Operations Manager, NCTU	Advice and development of NCTU working practice documents for *FaST-MP* relating to safety, quality and monitoring.
Antony Colles	Senior Data Programmer, NCTU	Development of the *FaST-MP* REDCap online interactive database to randomise, unblind and schedule study visits. Lead author of the *FaST-MP* data management plan.
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Katharine Goodall	Data Assistant, NCTU	Development and review of case report forms for *FaST-MP.*
Sue Robinson	Research Assistant, Respiratory Research Group NNUH	Assistance with arranging and undertaking patient research visits (both activity monitor study (chapter 3) and *FaST-MP*), data entry onto REDCap system.
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Statement of jointly authored publications

The research reported is my own work, which was carried out in collaboration with others as follows:

Chapter 1: Written by Chris Atkins

Chapter 2: Chris Atkins was the lead author of the following published paper:

Atkins C, Wilson AM. Managing fatigue in sarcoidosis – A systematic review of the evidence. Chronic Respiratory Disease 2017; 14(2): 161-173

CA designed the search strategy, registered the review with PROSPERO, performed the initial and subsequent literature searches, performed data collection and analysis and wrote the manuscript. AMW reviewed the search strategy, reviewed the search results for accuracy, performed a review of the data for data accuracy and quality, and reviewed the final manuscript including responding to peer review for the final manuscript.

Chapter 3: Chris Atkins was the lead author of the following published paper:

Atkins C, Jones AP, Wilson AM. Measuring activity in patients with sarcoidosis – a pilot trial of two wrist-worn accelerometer devices. Sarcoidosis Vasculitis and Diffuse Lung Diseases 2018: 35; 62-68

CA designed and led this study. The initial protocol was drafted by CA under the guidance of AMW and APJ. CA recruited and consented all patients, analysed the data and wrote the initial manuscript with input from AMW and APJ.

Chapter 4: Chris Atkins was the lead author of the following published paper:

Atkins C, Fordham R, Clark AB, Stockl A, Jones AP, Wilson AM. Feasibility study of a randomised controlled trial to investigate the treatment of sarcoidosis-associated fatigue with methylphenidate (FaST-MP): a study protocol. BMJ Open 2017; 7(12): e018532

CA designed and led this study. The initial study protocol was drafted by CA with input from RF, ABC, AS, APJ and AMW. Associated study documents (PIS, consent forms, non-validated questionnaires, and case report forms) were designed by CA. CA gained REC and MHRA approvals, and subsequent amendments. CA drafted the manuscript with comments and editing additionally provided by RF, ABC, AS, APJ and AMW.

Chapter 5: Written by Chris Atkins

Chapter 6: Written by Chris Atkins

Chapter 7: Written by Chris Atkins

Chapter 8: Written by Chris Atkins

Chapter 1: *Introduction and Background - Sarcoidosis and Fatigue*

1.1 Overview of Sarcoidosis

Sarcoidosis is a multi-system disease characterised by non-caseating granulomas which affects all ethnic groups and ages. Disease presentation is highly variable as any organ system can be affected, although pulmonary manifestations are most common. Non-specific and constitutional symptoms, including fatigue, frequently occur. The disease can present acutely and may spontaneously resolve but for some patients follows a chronic disease course requiring treatment. In these cases, management is typically with corticosteroids or other immunosuppressant medications. For the majority of patients, the condition does not significantly affect survival but may have an impact upon quality of life; for this reason, management of symptoms is of great importance in patients with sarcoidosis.

1.2 History of sarcoidosis

Sarcoidosis was first described by Jonathan Hutchinson, a London surgeon (1, 2). In 1877 Hutchinson described the case of a coal-wharf worker with symmetrical, non-tender, purple skin plaques affecting his hands and legs (3). Hutchinson later described the disease as a "form of skin disease which has - hitherto escaped special recognition" (4). Caesar Boeck, a Norwegian dermatologist, described 24 cases of "benign miliary lupoids," labelling the condition "sarkoid" due to the macroscopic resemblance to sarcoma but with a benign disease course. Some of the cases had involvement of other systems, including the lungs, lymph nodes, spleen, conjunctiva and bones (5). The common acute presentation of sarcoidosis was first described by Sven Löfgren, a Swedish clinician. He described the link between erythema nodosum and bilateral hilar lymphadenopathy, as well as the excellent prognosis of this presentation of the disease (6).

Differentiation between sarcoidosis and tuberculosis was difficult. In 1941, Morten Kveim described a reaction to intradermal inoculation of lymphoid tissue (taken from sarcoidosis patients) which did not occur in subjects without the disease but occurred in 12 out of 13 patients with sarcoidosis (7). This test remained in clinical use for over 50 years (8, 9). The test had a less than 1% false positive rate in non-

sarcoidosis cases (10, 11), as opposed to stimulating agents, including mycobacteria, beryllium and silica, which produce a reaction in almost all patients (12). The Kveim test is no longer used for the diagnosis of sarcoidosis, with modern diagnosis made using clinical, imaging and histological samples.

1.3 Epidemiology

There is significant variability in incidence by ethnic group and geographical region; the highest incidence is seen in African American and Northern European populations (13, 14). Table 1 shows the varying incidence of sarcoidosis across the globe, presenting the results from a literature search of the Medline electronic database the using the search terms *"sarcoid" OR "sarcoidosis" OR sarcoidosis [MeSH Terms] OR Sarcoid* (truncation)* ***AND*** *incidence.* Cases of sarcoidosis appear to be presenting at a later age. Work from the 1980s suggested a peak incidence in those aged 20 to 34 (15); more recent evidence from a similar population in Northern Europe revealed a mean age of 51.2 years at diagnosis (14), with similar changes seen between 1974 and 2012 in Japan (16).

Table 1 *- Incidence of Sarcoidosis worldwide, ordered by continent*

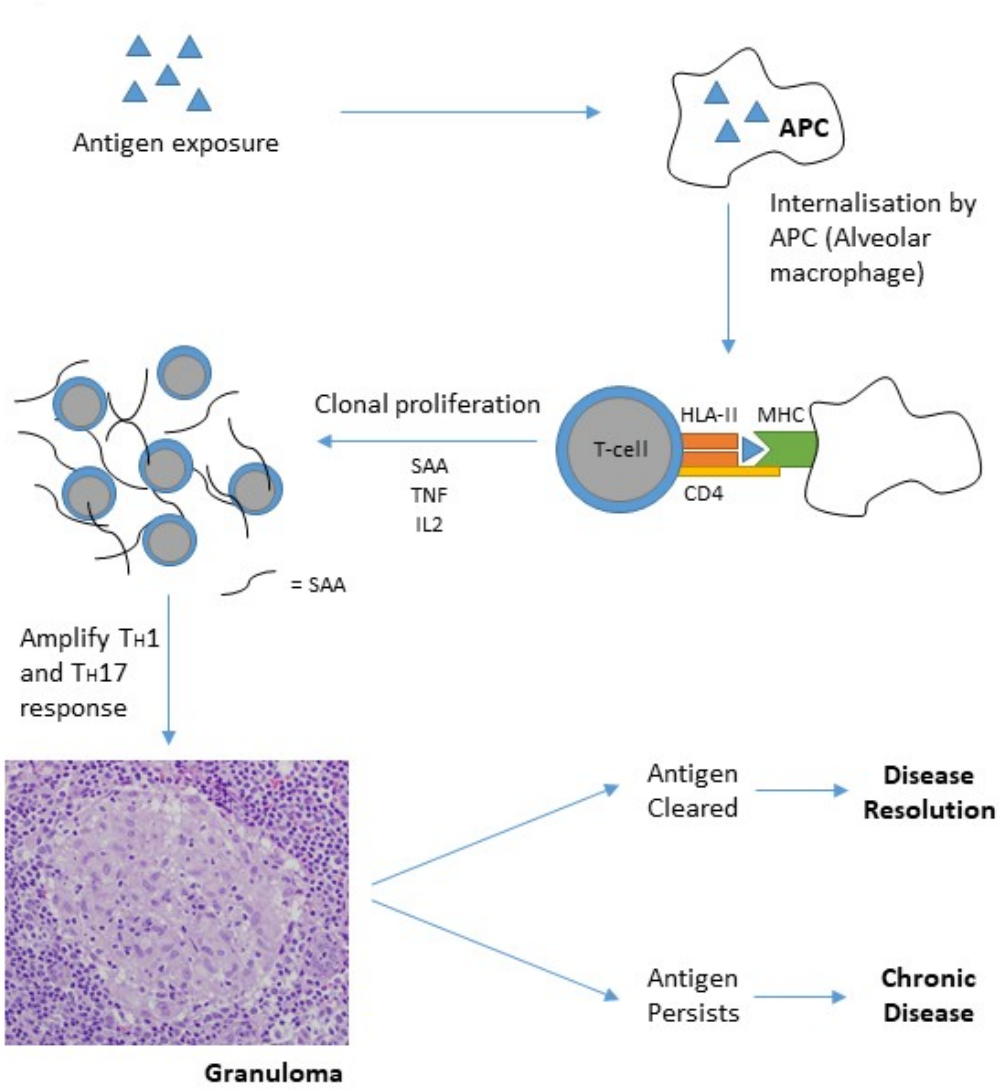
Study Year(s) of data Country	**Annual incidence Rate** (per 100,000 population)	**Mean age at diagnosis** (years)	**Male Sex**	**Ethnicity**	**Comments**
Europe					
Parkes et al (17) 1962-1976 1977-1983 UK (Isle of Man)	3.5 (3.3–3.8) *(72-76)* 14.7 (9.6-18.0) *(77-83)*	Not stated	46.4% *(1972-76)* 45.4% *(1976-83)*	Not stated	Cases diagnosed by kveim test after 1977. Active case finding; reminder to GPs and radiologists given in 1977 about the condition.
Hillerdal et al (15) 1966-1980 Sweden (Uppsala)	19.0 (14.7-23.2)	Men – 34 Women – 45 (Median ages)	42.4%	Not stated	Identified cases in three ways: (1) CXR at health screening every (>50% cases), (2) Chance finding (e.g. incidental finding on CXR), (3) Presentation with symptoms
Poukkula et al (18) 1970-1981 Finland	15.0	Not stated	47.5%	Not stated	Cases identified by 3-yearly CXR screening and followed-up in hospital
Byg et al (19) 1980-1994 Denmark	7.2	41.4 *(Median ages – Men 38, Women 45)*	50.9%	Not stated	Peak incidence in men aged 30-34 years 14.8/100,000); two similar peaks were seen in female cases between 25-29 and 65-69 years of age (10.5 and 11.0/100,000 respectively)
Karakatsani et al (20) 1981-2003 Greece	1.07	Not stated	Not stated	Not stated	All cases registered across multiple centres, covering approximately 60% of Greek population
Gribbin et al (21) 1991-2003 UK	5.0	Not stated	47.3%	Not stated	Longitudinal data from primary care records
Thomeer et al (22) 1992-1999 Belgium	0.26	Not stated	Not stated	Not stated	
Tinelli et al (23) 2000-1/2005 Italy	Not stated	52.4 +/- 14.5 (Range 11 – 87)	45.1%	Not stated	Italian ILD registry; incidence not reported
Deubelbeiss et al (24) 2002-2005 Switzerland	7.0	45.0 +/- 15.0	Not stated	Not stated	Diagnosis taken from federal statistics
Arkema et al (14) 2003-2013 Sweden	10.4-14.8	51.2 +/-16.0	53.4%	Not stated	Register-based; ICD-8, -9 or -10 codes for sarcoidosis
Kowalska et al (25) 2006-2010 Poland	5.1-7.3	42.4-46.2 years	Not stated	Not stated	Retrospective data from the *National Health Fund* using ICD-10 codes

Study Year(s) of data Country	**Annual incidence Rate** (per 100,000 population)	**Mean Age at diagnosis** (years)	**Male Sex**	**Ethnicity**	**Comments**
USA					
Gorham et al (26) 1975-2001 USA (US Navy)	Overall: 7.1 Black: 24.9 White: 3.5 *(All were hospitalised cases)*	Not stated	Not stated	Not stated: both white and black ethnicities included in cohort	US naval records for old and new cases; incident cases identified using database of inpatient data records
Ungprasert et al (27) 1976-2013 USA (Minnesota)	10.0	44.2 +/-1 13.8	48%	Caucasian – 92% African-American – 4% Asian – 1.5% Native American – 0.5% Other – 2%	Physician diagnosis supported by histopathology and radiographic features with compatible clinical presentation.
Dumas et al (28) 1989-2011 USA (nationwide)	Black 43.0 White 11.0	48.0 *(range 28-63yrs)*	0%	95.9% White; 1.8% Black; 2.3% other	Data from Nurses' Health Study II – prospective study of 116,430 US female nurses
Rybicki et al (29) 1990-1994 USA (Detroit)	Black: 35.5 White: 10.9	38.6 years	35.3%	39.6% Caucasian 60.4% African-American	Records from Health Maintenance Organisation data, using ICD-9 code
Cozier et al (13) 1995-2007 USA (nationwide)	71.0	38.0 *(Median)*	0%	100% African-American women	Data from Black Women's Health Study – prospective study of 59,000 participants
Other					
Haraldsdottir et al (30) 1981-2003 Iceland	3.84 (2.8 during 1981-1992, 5.0 during 1993-2000)	50.8 (women) 47.5 (men)	48.1%	Not stated	All cases histologically proven
Kim (31) 1992-1999 South Korea	0.13	Not stated	35.4%	Not stated	Peak decade of onset was 30-39 (33% of cases). All cases biopsy-proven, from 58 hospitals. Clinical manifestations similar to "western pattern"

1.4 Pathogenesis and aetiology

The pathological hallmark of sarcoidosis is the presence of non-caseating epithelioid granulomas, leading to distortion of tissue architecture which may result in organ dysfunction (32). The granulomas form due to an inability to destroy and eliminate an antigen (33), which is internalised by macrophages and processed into peptides presented to CD4 T-cells (32). These interactions initiate granuloma formation and promote local proliferation of a clonal population of T cells, further stimulated by the trapping of antigens by serum amyloid A (SAA) and other proteins, establishing the nidus of the granuloma (33). A graphical overview of granuloma formation is shown in Figure 1. Further release of immune-mediators, including tumour necrosis factor (TNF), leads to continued proliferation due to amplified CD4 type 1 helper T cells (T_H1) response. In tissue surrounding the central core of the granuloma an increase in T_H17 cells is seen (34), which secrete potent pro-inflammatory cytokines including interferon gamma. The ability to clear the antigen may determine the subsequent disease course; the T_H1 response may be effective at gaining immune control of the initial insult but the accumulation of SAA and other proteins as an antigen trap can sequester further circulating antigens and cause an ongoing inflammatory response (35).

Figure 1 *- Granuloma formation in sarcoidosis*



APC = Antigen presenting cell; MHC = Major histocompatibility complex; HLA-II = Human leukocyte antigen – Class II; CD4 = Cluster of differentiation 4; SAA = Serum Amyloid A; TNF = Tumour Necrosis Factor; IL2 = Interleukin 2; T_H1 = T helper 1 cell; T_H17 = T helper 17 cell

Granuloma image in public domain (https://commons.wikimedia.org/wiki/File:Granuloma_20x.jpg)

Whilst the pathogenesis of the disease may be uniform, the driving aetiology for the development of sarcoidosis remains obscure. Data from epidemiological research supports an infective agent as a possible trigger, with clusters linked by time or geographical location (36, 37). Potential identified triggers include; Mycobacterial Catalase G (mKatG) (38, 39), catalases from *Proprionibacterium* (KAT, particularly from *P acnes*) (39-41), inorganic dusts and metals (including aluminium, zirconium, titanium and beryllium) (42-44), and exposure to biomaterials such as wood pollen and organic dusts (45, 46).

Genetic factors also play a role. Clustering within families is seen, with elevated risk observed in first- and second-degree relatives, particularly siblings who have a relative risk 4.7 for developing the disease (47). Registry-based twin studies show an 80-fold increased risk of developing sarcoidosis in monozygotic twins; in dizygotic twins the relative risk is 7 (48), not dissimilar from the risk in non-twin siblings observed in other studies (47).

Genetic loci associated with sarcoidosis include; *BNTL2* (49-51), *ANXA11* (52) and multiple areas of the HLA region on chromosome 6 (53), including HLA-B, HLA-DPB1, HLA-DRB1 and HLA-DQB1 (54). The polymorphisms HLA-DRB1*01, DRB1*03 and DRB1*14 have been associated with Löfgren's syndrome; DRB1*07, DRB*14 and DRB1*15 are associated with non-resolving disease whereas DRB1*01 and DRB1*03 protect against persistent disease (55). Recently, additional non-HLA loci with a prominent role in the IL12/23 signalling pathway have been identified (54). IL12 is a T-cell stimulating factor that leads to differentiation of native T-cells into T_H1 cells (56) whilst IL23 induces differentiation to T_H17 cells (57).

1.5 Clinical manifestations of sarcoidosis

The frequency of different patterns of organ involvement appears to vary between countries. Table 2 shows the results of a literature search of the Medline electronic database for studies describing the presentations of sarcoidosis and the oragsn affected. The most frequent organ affected is the lungs, occurring in 95% of cases of sarcoidosis, most commonly consisting of hilar lymphadenopathy (58). The association of bilateral hilar lymphadenopathy with erythema nodosum (EN) or bilateral ankle arthritis (Löfgrens syndrome) has been recognised as an acute and typically benign manifestation of sarcoidosis (59, 60). Longitudinal follow-up of these cases has reinforced the picture of these acute manifestations largely being benign; in one study only 11 of 133 patients (8%) had active disease within 2 years and only eight patients (6%) developed a recurrence of sarcoidosis(61). Beyond this well recognised syndrome, as a multi-system disease sarcoidosis can affect any organ or system within the body.

Recently, a cluster analysis of 2,163 Caucasian patients with sarcoidosis identified five specific patterns of organ involvement (62). These patterns were 1) abdominal involvement (renal, spleen and hepatic involvement); 2) ocular-cardiac-cutaneous-CNS involvement, also frequently showing cutaneous manifestations, salivary gland involvement and fatigue; 3) Musculoskeletal-cutaneous involvement, which were more likely to present acutely and more likely to suffer fevers, night sweats, weight loss or arthralgia; 4) Pulmonary-lymphonodal, where lung function was worse but skin and musculoskeletal involvement was less frequent; and 5) Extrapulmonary disease, which was similar to cluster 4 but associated with no impairment to lung function. The study (62) was the first to suggest specific patterns of organ involvement beyond the eponymous acute presentations and may enable better prognostication beyond existing staging systems.

***Table 2** - Patterns of organ involvement across cohorts of sarcoidosis patients around the world*

Country of Study	***USA (58)***	***Finland[a] (63)***	***Japan[a] (63)***	***Turkey (64)***	***Europe[b] (62)***
Total patients	736	600	686	293	2163
Mean Age (yrs)	*not reported*	41.4	30.3	44.0	47.0
Caucasians (%)	53.4	*not reported*	*not reported*	*not reported*	100
Female (%)	63.6	58.8	54.8	67.5	59.6
Organs Involved (%)					
- Lungs	95.0	93.8	76.4	95.2	75.5
- Skin *(excl. erythema nodosum)*	15.9	-	-	16.0	16.1
- Lymph node	15.2	23.3	20.0	-	77.0[d]
- Eye	11.8	4.5	50.1	3.4	7.8
- Liver	11.5	0.3	0.9	3.8[c]	4.9
- Erythema nodosum	8.3	17.0	0.4	21.5	-
- Spleen	6.7	4.2	0.0	4.1[c]	3.9
- Neurological	4.6	-	-	-	3.4
- Parotid/salivary	3.9	-	-	1.4[c]	-
- Bone marrow	3.9	-	-	-	-
- Calcium	3.7	-	-	-	-
- ENT	3.0	-	-	-	-
- Cardiac	2.3	0.3	4.5	-	3.2
- Renal	0.7	-	-	-	3.3
- Bone/Joint	0.5	-	-	28.7	9.6
- Muscle	0.4	-	-	4.8	7.5
- Gastrointestinal	-	-	-	-	0.6
- Genital	-	-	-	-	0.2
- Other	-	8.7	1.0	-	-

[a] Includes both familial and non-familial cases of sarcoidosis

[b] Centres included Serbia. Germany, Italy, The Netherlands, Poland, UK, Czech Republic, Ireland, Iceland, France, Croatia, Hungary, Belgium,

[c] Paper presents rates of organ enlargement but does not specify whether organ directly affected by sarcoidosis on radiology or biopsy.

[d] Intrathoracic lymph nodes only; extrathoracic lymph nodes involved in 11.3% of cases

1.6 Diagnosis

Chest X-ray (CXR) is the most common method of identifying pulmonary sarcoidosis and remains an important investigation. In the ACCESS study investigating presentations of sarcoidosis, 91.7% of patients had abnormalities on their CXR(58). The most widely used system for staging sarcoidosis by CXR is the Scadding criteria, a score initially proposed in the 1960s from a review of 136 cases (65) and amended in 1983 (66). The score is displayed in Table 3 below alongside the initial four groups as described by Scadding in 1961.

Table 3 *- Chest X-ray staging systems for sarcoidosis*

Stage	Description – DeRemee (1983) (66)	Description – Scadding (1961) (65)
0	Normal chest radiograph	*Not mentioned*
I	Lymph node enlargement (hilar, mediastinal) only	Enlarged hilar lymph nodes only
II	Lymph node enlargement and parenchymal opacity	Mottled shadowing in the lungs with enlarged hilar lymph nodes, either at present or known to have been present in the past
III	Parenchymal opacity, no evidence of fibrosis or lymph node enlargement	Mottled shadowing in the lungs, without present or available past evidence of enlargement of hilar lymph nodes
IV	Lung fibrosis present	Radiographic and clinical features suggesting fibrosis, usually in addition to mottled shadowing

Further imaging, usually with computed tomography (CT), is recommended where the findings on CXR are atypical or subtle, or where complications such as pulmonary hypertension or bronchial stenosis are suspected (67, 68). CT imaging can guide where biopsies should be taken from, and disease extent as assessed by CT imaging correlating with the likelihood of a positive biopsy from the lung parenchyma (69). After diagnosis there is little benefit offered by CT scanning over

conventional CXR monitoring for follow-up of the disease unless complications occur (70).

Magnetic resonance imaging (MRI) has no current role for the investigation of pulmonary sarcoidosis for a number of reasons, including low proton density of pulmonary tissue and movement during respiration resulting in artefacts (71). However, MRI has an important role when suspecting cardiac sarcoidosis due to its high sensitivity for identifying disease affecting the heart. For this reason it is recommended as the investigation of choice for patients with suspected cardiac sarcoidosis (72, 73).

Positron emission tomography (PET) scanning, in combination with CT (PET-CT), allows cross-sectional imaging with overlay of metabolic activity to determine areas of activity in sarcoidosis (74), although it is reserved for atypical and complex cases, including for follow-up of response to treatment (75). It has a role for identifying cardiac sarcoidosis and is similar in accuracy to MRI, with the added benefit of being able to be performed where a non-MR compatible pacemaker is in situ (76).

A firm diagnosis of sarcoidosis is usually made from biopsy specimens of affected organs, the exception being in patients presenting with acute presentations of sarcoidosis consistent with Löfgren's syndrome (77). Biopsies are frequently taken from the lungs, given the frequency with which the organ is affected. In patients with parenchymal disease (stage II or III disease), transbronchial lung biopsies (TLBs) obtained during bronchoscopy offer good diagnostic yield (78-80).

More recent developments in bronchoscopy have led to the widespread use of endobronchial ultrasound (EBUS), which enables safe transbronchial needle aspiration (TBNA) of enlarged lymph nodes or masses adjacent to airways. The GRANULOMA trial (81) compared TLBs with EBUS-TBNA sampling in stage I or II sarcoidosis, with the diagnostic yield of EBUS-TBNA significantly higher than TLBs (74% vs 48%). Although seemingly less effective than EBUS-TBNA at acquiring histological samples and confirming the diagnosis, traditional bronchoscopy and TBLB retains a place in the diagnosis pathway due to the inability to use EBUS in patients without mediastinal lymphadenopathy.

1.7 Treatment for Sarcoidosis

Not all patients with sarcoidosis require treatment; pharmacological management is reserved for patients with organ dysfunction or to improve quality of life (82). Current UK guidelines recommend pharmacological treatment is not warranted for asymptomatic stage I disease, or for stage II or III disease when lung function is stable with only mild abnormalities (83).

Present guidelines from the British Thoracic Society (BTS) recommend oral corticosteroids as the first-line agent when treatment is required. The BTS guidelines suggest that steroids are used for patients with progressive disease (radiologically or on lung function), or where disease is threatening other organs or leading to significant symptoms; in these cases a dose of 0.5mg/kg/day equivalent of prednisolone is recommended, with reduction of the dose over a period of 6-24 months (83). The American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Diseases (WASOG) also recommend oral corticosteroids as initial therapy where required for progressive symptomatic disease, suggesting an initial dose of 20-40mg/day of prednisone or equivalent for at least 12 months (84). Evidence of benefit from corticosteroids is mixed; a meta-analysis found the only significant outcome improved by steroids was in CXR features, although the authors concluded that the data supports use of oral corticosteroids for patients with stage 2 or stage 3 disease (85).

The possible benefit must be balanced against the short and long-term side effects of corticosteroids, including increased risk of osteoporosis and subsequent fracture (86), weight gain (87), impaired quality of life and increased fatigue (88), and possibly even an increased risk of death (89).

In patients where disease progresses despite steroids, when prolonged courses of steroids are required, or when steroids cannot be used or tolerated due to side effects it is recommended that other immunosuppressant medications are used, with methotrexate or azathioprine the preferred options (83, 84). An additional antimetabolite, leflunomide, is well tolerated and appeared as effective as

methotrexate (90, 91). At present leflunomide is reserved for those intolerant of azathioprine or methotrexate (83).

Mycophenolate mofetil (MMF), an inhibitor of T- and B-cell replication through depletion of guanosine nucleotides (92), has been used to treat sarcoidosis with evidence of steroid sparing activity (93, 94). The use of MMF does not appear beneficial if azathioprine or methotrexate have failed to stabilise disease but can be used if they have not been tolerated; it is presently not mentioned in current guidelines as the trial evidence has only been released since the last updates (83).

The antimalarials chloroquine and hydroxychloroquine are alternative second line therapy for sarcoidosis in some cases (83). The use of hydroxychloroquine alongside prednisolone has been shown to be effective for hypercalcaemia and hypercalciuria in sarcoidosis (95, 96); this is likely due to the reversal of abnormalities in vitamin D3 metabolism, inhibiting synthesis of 1,25-dihydroxyvitamin D3 by pulmonary alveolar macrophages responsible for hypercalcaemia via vitamin-D dependent pathways (97).

Monoclonal antibodies are available for clinical use which block the actions of TNF-alpha, a cytokine known to be involved in the granulomatous processes behind sarcoidosis (98, 99). Infliximab, adalimumab, golilimumab and etanercept have all been trialled in sarcoidosis.

Infliximab has been shown to have some ability to reduce inflammation in sarcoidosis, demonstrated on PET scanning (100). It has been suggested that infliximab is most effective for extra-pulmonary sarcoidosis, especially in those with neurological, cardiac, skin or upper respiratory tract involvement (101). However, adverse events are common with infliximab. Infection is the most common adverse event (101-103), although reactions and antibody-formation against infliximab can also occur (101). The formation of anti-infliximab antibodies has been shown to correlate with poorer clinical responses (104). Adalimumab can be used where infliximab has failed, including where antibodies against infliximab have been produced, with trial evidence suggesting benefit in patients with ocular involvement as well a steroid-sparing effect (105). More recently, golilimumab, and

ustekinumab (a monoclonal antibody inhibiting IL12 and IL23) have been trialled in patients with ongoing steroid requirements; no differences were seen between golilimumab, ustekinumab and placebo after 16 weeks of therapy (106).

Furthermore, despite the anti-sarcoidosis activity of TNF-blocking drugs, there are a number of reports of patients developing paradoxical sarcoidosis-like lesions during treatment with anti-TNF-alpha therapies for other conditions. A review of the literature identified 90 cases of such paradoxical reactions, most commonly occurring with etanercept (53 cases, 59%) but also with infliximab and adalimumab (107). The most recent UK interstitial lung disease guidelines recommend that these drugs are used with caution and only when there are no other alternatives (83).

1.8 Prognosis and mortality

The disease course of sarcoidosis is highly variable, although some prediction is possible based upon the disease stage. Up to 90% of cases with stage I disease, including those with the acute manifestation of Löfgren's syndrome have spontaneous remission, remission in stage II disease occurs in up to 70% of cases, while less than 40% of cases in stage III will remit (15, 108). The recent identification of disease phenotypes, discussed in section 1.5, suggests that prognosis and need for treatment is dependent on more than simple CXR appearances. In the absence of cardiac or neurological involvement, rapid or extensive pulmonary fibrosis, or pulmonary hypertension, the disease course is frequently mild and prognosis is excellent (27).

Mortality rates in cohorts with sarcoidosis have been claimed to be between 1 and 5% (84). Variability in mortality is seen between patients referred to hospital settings and those within the general population. A systematic literature review published in 2002 estimated mortality attributable to sarcoidosis in "referral settings" (secondary care/hospital care) to be 4.8% from 2,838 cases within seven studies, approximately ten times the rate seen in sarcoidosis patients within wider population samples (0.5% of 812 cases across three studies) (89). The estimate of mortality in the review was described as "an imprecise measure" and is not a

standardised rate. The review also investigated possible factors predicting increased mortality; no relationship with ethnicity was seen but the author concluded that a lower threshold for administering corticosteroids is associated with an increased risk, independent of disease severity.

1.9 Fatigue and Sarcoidosis

Fatigue can be defined as "the awareness of a decreased capacity for physical and/or mental activity due to an imbalance in the availability, utilization, and/or restoration of resources needed to perform activity" (109). Whilst it is a subjective symptom it is experienced by everyone to varying degrees throughout the population, often as a temporary complaint due to psychosocial factors including work patterns, but also related to psychosocial problems or physical disease (110). Fatigue specifically related to underlying sarcoidosis, termed a "post-sarcoidosis chronic fatigue syndrome", was described by DG James in 1993, who stated "up to 5 per cent of patients, seemingly recovered from active sarcoidosis, develop a post-sarcoidosis chronic fatigue syndrome" (111). The description included general myalgia, debilitating fatigue sleep-reversal and poor sleep quality, all occurring in the absence of physical signs. The presence of fatigue within this syndrome has a significant impact on both the physical and psychological burden of disease (Figure 2), negatively affecting an individual's quality of life and function.

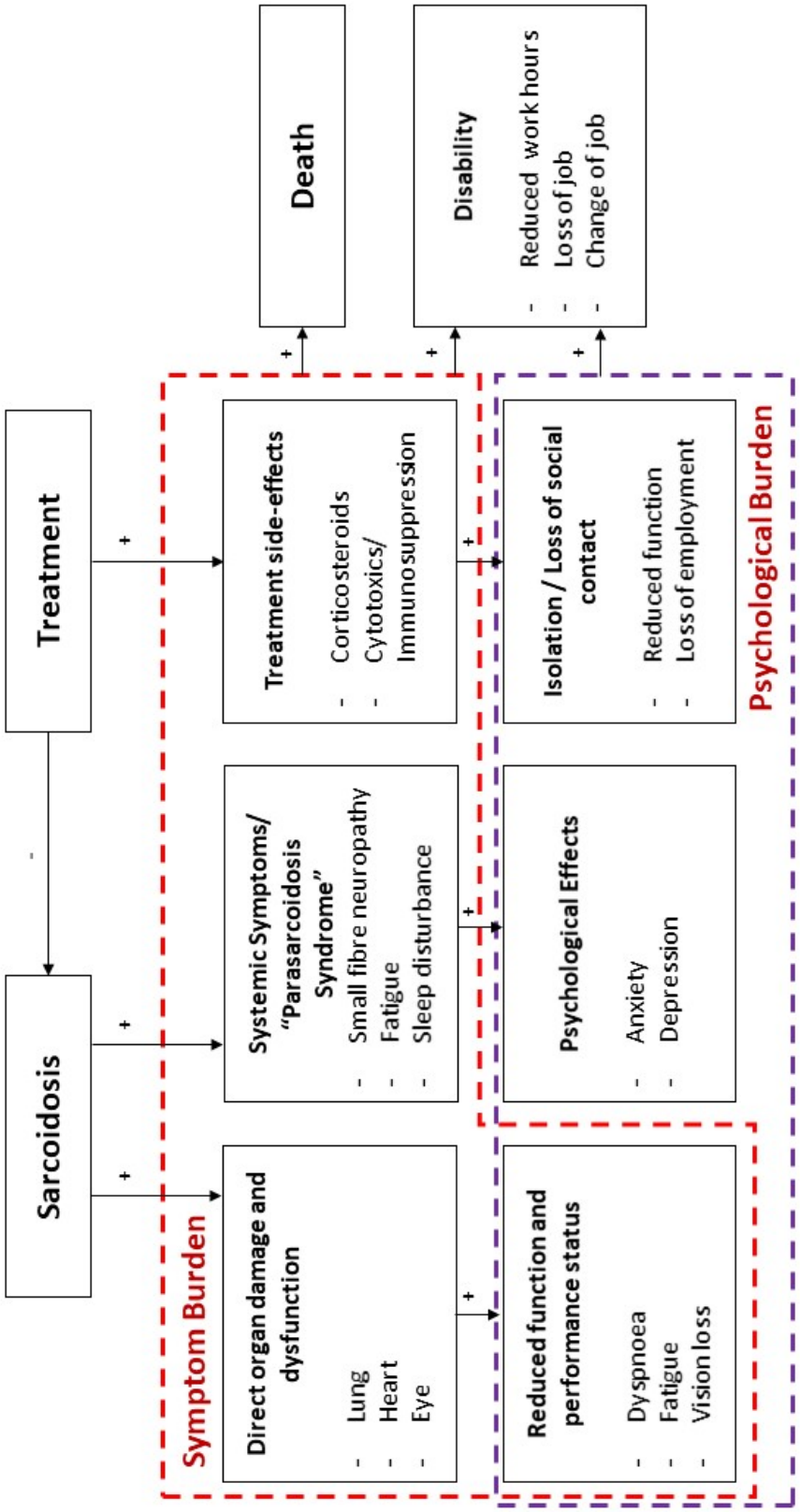
Fatigue is a chief complaint amongst patients with sarcoidosis. In a large cohort of sarcoidosis patients in the Netherlands (837 members of the Dutch Sarcoidosis Society and 68 outpatients), 80% of sarcoidosis patients reported significant fatigue using a validated fatigue measurement scale (112). A cross-sectional study of 121 Dutch sarcoidosis patients and 126 American sarcoidosis patients revealed similar levels of fatigue. Using the same Fatigue Assessment Scale (FAS), 83.2% of the Dutch cohort and 74.6% of the American cohort reporting FAS scores >21, indicating significant fatigue, although more Dutch patients reported FAS scores of >35 (37.8% vs 19.0%, p=0.004), consistent with severe fatigue (113). A previous review reported frequencies of fatigue of between 33% to over 80% of patients

(114), reinforcing the importance of this symptom in sarcoidosis cohorts. It appears unrelated to disease severity and clinical parameters, with no clinical or physiological variables able to predict the presence or severity of fatigue (115).

Sarcoidosis is not the only systemic disease associated with fatigue. Fatigue is also a problem in other chronic diseases including inflammatory bowel disease (116), rheumatoid arthritis and other rheumatic diseases (117), cancer (118), HIV (119), primary sclerosing cholangitis (120) and multiple sclerosis (121). Fatigue in sarcoidosis may be multifactorial in origin and a number of hypotheses for this fatigue have been put forward, including subclinical disease activity, post-inflammatory effects on the central nervous system, treatment-related side-effects or disorders of sleep (122).

Treatment of fatigue is difficult and often unresponsive to standard treatment regimens for sarcoidosis activity, making it a problematic symptom for the physician to treat. Multiple treatment options have been suggested by researchers which are discussed in greater detail in chapter 2.

Figure 2 *- Interaction between physical and psychological symptoms within sarcoidosis*



Adapted from Gerke et al.
Disease burden and variability in sarcoidosis. Ann Am Thorac Soc 2017;14(6):S421-S428

Proposed mechanisms for sarcoidosis-associated fatigue

Systemic inflammation and cytokine release

As sarcoidosis is a disease characterised by granulomatous inflammation that can occur within any system of the body, it has been suggested that the presence of ongoing inflammation is related to constitutional features, including fatigue (123). One small study reported the results of a cross-sectional assessment of 38 patients with sarcoidosis, showing that those with fatigue (n=25 using the energy and fatigue facet of the World Health Organization Quality of Life assessment instrument) had higher levels of C-reactive protein (CRP; 11.4±6.8mcg/ml vs 3.2±6.8mcg/ml, p<0.0001) compared with non-fatigued sarcoidosis patients (123). Another study compared TNF-alpha and interleukin-1 beta (IL-1 beta) levels between 22 patients with sarcoidosis and 22 control subjects; those with sarcoidosis exhibited higher general fatigue scores measured by the multidimensional fatigue inventory (15.5+/-4.9 compared with 7.3+/-3.2, p<0.0001) and higher resting TNF-alpha levels (1.72pg/ml compared with 1.21pg/ml in controls, p=0.0008), with no difference in IL-1 beta levels between groups (124). Improvements observed in fatigue scores when targeting TNF-alpha with infliximab or adalimumab further suggests a possible role for this cytokine in the aetiology of sarcoidosis-associated fatigue (105, 125). It has been shown to have a role as a pro-inflammatory cytokine in sarcoidosis, with evidence of increased production of TNF-alpha and TNF-alpha receptor-1 and -2 by alveolar macrophages in ten patients with sarcoidosis (98, 126).

These small studies of patients provide limited evidence to support the systemic inflammation theory but has led on to further work investigating the use of ^{18}F-2-fluoro-2-deoxy-D-glucose (^{18}FDG) PET-CT. A review of 188 patients with sarcoidosis that underwent a PET scan revealed that 137 had evidence of inflammation, most commonly in the mediastinal lymph nodes (127). Further work suggests that inflammatory activity can persist in the absence of commonly measured serum markers of inflammation (128). Although this study did not investigate the presence of fatigue in these patients, another study of 12 patients with sarcoidosis received six cycles of infliximab with pre- and post-therapy PET scans. Nine of the patients in

this trial reported fatigue pre-intervention, although no validated measurement of fatigue pre- and post-intervention was undertaken. All patients reported subjective improvement in symptoms, including fatigue, post-treatment. All but one patient showed an improvement in their PET scan measures of inflammation, though one patient showed increased inflammatory changes post-treatment and yet reported improved fatigue (129).

Small fibre neuropathy and autonomic dysfunction

Involvement of the nervous system by sarcoidosis is rare; one recent meta-analysis of previous cohorts reported 5% of cases develop neurosarcoidosis (130). Direct involvement of the peripheral nerves is a rare cause of peripheral neuropathy. One case series of 3475 cases with peripheral neuropathy undergoing nerve biopsy revealed involvement by sarcoidosis in only 11 (0.31%) patients (131). Small fibre neuropathy appears to occur more frequently, with one cross-sectional study showing that 44% of patients with sarcoidosis suffered small fibre neuropathy, confirmed using intra-epidermal nerve fibre density (132). In these cases, the involvement of small peripheral fibres (myelinated Aδ or unmyelinated C fibres) leads to problems with pain, dysaesthesia, disturbed sense of temperature and possible autonomic involvement if the autonomic nervous system is affected; the mechanisms behind this are unclear (132). There is significant overlap between fatigue and symptoms of small fibre neuropathy. One series of 57 patients revealing that 49.1% of cases (28 patients) suffered constitutional symptoms including fatigue (133). Another study identified that small-fibre neuropathy symptoms were more likely to occur in patients with worsening fatigue; 94% of patients with continuous fatigue reported symptoms of small-fibre neuropathy (134).

It has also been suggested that involvement of the autonomic nervous system, as occurs in small-fibre neuropathy, can lead to the development of chronic fatigue. The autonomic nervous system controls sympathetico-vagal balance through multiple pathways (135). Observations in chronic fatigue syndrome (CFS) have shown differences in autonomic function, measured by heart rate response during

tilt-table test, compared with healthy controls (136, 137). A pattern of sympathetic hyperactivity is observed in the setting of decreased parasympathetic activity (135). The same pattern of autonomic dysfunction, notably a shift of sympatho-vagal balance in favour of reduced parasympathetic activity and a relative sympathetic predominance, is seen in chronic sleep deprivation in healthy subjects (138, 139). Whilst a direct link between altered autonomic function and fatigue has not been drawn in patients with sarcoidosis, autonomic dysfunction has been identified in recent studies. One study investigated circadian blood pressure in 63 normotensive patients with sarcoidosis compared with 49 controls looking for alterations in blood pressure patterns suggestive of autonomic dysfunction; 80% of the sarcoidosis group had these alterations, compared with 50% of controls ($p=0.002$) (140). Another study investigating ECG changes consistent with autonomic dysfunction in 31 sarcoidosis patients without cardiac involvement by the disease, compared with 30 age-matched controls; the results revealed heart rate variability consistent with autonomic dysfunction, specifically increased sympathetic activation, in the patients with sarcoidosis (141). Both of these studies were small but the results suggest a possible role for autonomic dysfunction in the development of fatigue in patients with sarcoidosis.

Depression

Within cohorts of patients with sarcoidosis, increased depression and anxiety scores have been found to be associated with concomitant fatigue. One large study measured fatigue, anxiety and depression over an 18-month period in 443 patients with sarcoidosis in the Netherlands. The results showed that depressive symptoms and anxiety traits were both predictors for fatigue severity in multivariate regression analysis, although these symptoms were not found to fully overlap within the patient group (142). These findings have been replicated in other cross-sectional studies of factors affecting quality of life in patients with sarcoidosis (143), with one study of 588 patients with sarcoidosis showing that depressive symptoms predicted fatigue more than personality types indicating distress (type “D”), and that both depressive symptoms and fatigue were predictors of poorer overall

quality of life (144). One study investigating the impact of fatigue on multiple outcomes in sarcoidosis showed that fatigue was associated with both depression and anxiety symptoms (145). Furthermore, when investigating how anxiety and depression alter with types of fatigue (mild, intermittent or continuous fatigue), anxiety and depressive symptoms were most strongly associated with continuous fatigue, possibly moderating the nature or severity of fatigue suffered by patients (142).

The existing evidence only determines associations between depression and fatigue scores in a cohort of patients at a single time-point. This cannot determine whether the two symptoms are independent factors or whether there is interaction between them, and the direction and size of interaction between them. No studies have investigated pharmacological or psychological interventions for fatigue or depression in patients with sarcoidosis, therefore the change in depressive symptoms with improvement in fatigue, or vice versa, is unknown.

Sleep Disturbance

Poor subjective sleep quality in patients with sarcoidosis is associated with fatigue (146). Two mechanisms of sleep disturbance have been proposed as potential mechanisms for fatigue in patients with sarcoidosis; sleep-disordered breathing, including obstructive sleep apnoea (OSA) and periodic limb movement syndromes (PLMS), and abnormalities of circadian rhythm.

Previous research has suggested that sleep disordered breathing, specifically OSA, is more common in patients with sarcoidosis than the general population. Table 4 shows the results of a search of the Medline electronic data base, using the search terms *"sarcoid" OR "sarcoidosis" OR sarcoidosis [MeSH Terms] OR Sarcoid* (truncation)* ***AND "****sleep" OR "apnoea" OR "apnea" OR "OSA" OR " sleep-disordered breathing" OR Sleep Apnea, Obstructive [MeSH Terms].* Five studies (147-151) have investigated the prevalence of OSA in cohorts of patients with sarcoidosis using polysomnographs to diagnose OSA, one further study (152) recorded the prevalence of pre-diagnosed OSA in a large sarcoidosis cohort. The prevalence of

OSA seen amongst the five studies was between 8.6% and 66.6%, depending upon apnoea-hypopnoea index (AHI) criteria used. This is higher than the prevalence in the general population, where it is estimated to be between 3 and 17% (153). In one of the studies, electromyelography was performed to identify the presence of PLMS as well as OSA (151), with 7 (15%) of 46 patients having PLMS alone; PLMS was also present in 60% of the 20 patients who were found to have OSA on polysomnography. Although only including a small sample size, both of these results are significantly higher than the prevalence in the general population which has been estimated to be 7.6% (154).

***Table 4** – Summary of studies investigating prevalence of OSA in patients with sarcoidosis*

Study	Threshold for diagnosis of OSA	No. sarcoidosis patients included	No. sarcoidosis patients with OSA (%)	No. control pop-ulation	No. controls with OSA (%)	Notes
Turner GA et al. (147) *Sarc Vasc Diff Lung Dis 1997;14(1):61-4*	AHI >5 on poly-somnography	83	14 *(17%)*	91	3 *(3%)*	M>F, lupus pernio more frequent with sarcoidosis.
Verbraecken et al.(151) *Sarc Vasc Diff Lung Dis* 2004; 21(2):137-46	AHI >5 on poly-somnography	46	20 *(44%)*	None	--	12 of the OSA patients (44%) had periodic limb movement syndrome (PLM); 7 patients (15%) had PLM but not OSA.
Patterson KC et al. (148) Chest 2013;143(6):1562-8	Mild – AHI 5-15 Mod – AHI 15-30 Severe – AHI >30	62	Mild – 14 *(23%)* Mod – 12 *(19%)* Sev. – 20 *(32%)*	1,005	Mild – 210 *(26%)* Mod – 247 *(25%)* Sev. – 462 *(46%)*	Retrospective review of previously performed polysomnographs with lung function; sarcoidosis found to be an independent predictor of sleepiness (Epworth score)
Fleischer et al. (152) Respir Care 2014; 59(7):1086-1094	Cross-sectional study; diagnosis of OSA previously made prior to study, method of diagnosis and severity of OSA not reported	1,197	104 *(8.6%)*	None	--	Cross-sectional study including all patients (i.e. prior diagnosis of sarcoidosis). Patients "without" OSA not screened within trial to confirm.
Bingol et al. (150) Clin Respir J 2015; 9(1):14-21	AHI >5 on poly-somnography	29	15 *(51.7%)*	None	--	Patients with risk factors for OSA (BMI >30, upper respiratory tract pathology) were excluded – "low risk population". Higher rate in patients with parenchymal disease (n=10/15, 66.6% - seven had AHI 5-15/h, three had AHI >30) than without (n=5/14, 35.7% - all AHI 5-15/h).
Pihtili et al. (149) Sleep and Breathing 2016;17(4):1281-88	AHI >5 on polysomnography	15	10 *(66.6%)*	None	--	No division of results by severity within disease groups. 14/17 IPF patients and 10/18 scleroderma patients had AHI >5/hr

The development of OSA has been postulated to be due to two possible mechanisms; firstly, the use of steroids which can lead to obesity and OSA, or secondly the direct involvement of the upper respiratory tract by sarcoidosis. Four case reports have been published describing granulomatous involvement of the larynx and upper airway which led to the development of OSA in these patients (155-158). These cases were diagnosed by direct inspection of the oropharynx and larynx or through cross-sectional radiology of the upper airways. All required treatment with corticosteroids, with or without an additional agent, with good resolution of symptoms. Caution should be used with corticosteroids in this situation as there is a risk of worsening OSA, thus reduction to the lowest effective dose of steroids should be undertaken rapidly (159). Direct laryngeal involvement by sarcoidosis is a rare occurrence, with a reported frequency of less than 1% amongst 2319 patients attending the Mayo clinic and diagnosed with sarcoidosis (160).

An alternative cause for sleep disturbance in sarcoidosis may relate to disorders of circadian rhythm leading to abnormal sleep patterns. This may be related to the role of TNF-alpha as an inflammatory cytokine in sarcoidosis. The immune system function is impacted by central biological clocks, with immune cells and cytokine levels varying according to time of day and position within the sleep-wake cycle (161). TNF and its receptor has been shown in mouse studies to modulate circadian rhythm through actions on the suprachiasmatic nucleus (162). Abnormality of circadian rhythm in critically ill patients has been described, due to a number of causes including systemic inflammation and cytokine release (163). Whilst not investigated specifically in sarcoidosis, the known increase in TNF-alpha release and the improvement in fatigue with anti-TNF-alpha agents suggest a possible role for this in the development of fatigue, and the potential of TNF-alpha to influence circadian rhythm could therefore impact on the sleep-wake cycle. Furthermore, variations in TNF-alpha over the course of a 24-hour period are seen in other inflammatory conditions (164) and could provide a rationale for the variability of fatigue experienced in some patients with sarcoidosis (134).

Drug-induced symptoms

The role of drugs in the development of sarcoidosis-associated fatigue is contentious, but the most commonly used medication for suppression of disease activity (glucocorticoid steroids) is associated with numerous problems that can lead to fatigue. One population-based assessment of adverse events affecting 6,517 patients receiving glucocorticoids for various medical conditions demonstrated that increasing doses of glucocorticoids are associated with sleep disturbance, weight gain, elevated blood sugar and mood problems (165). All these factors showed strong dose-dependent association, with sleep disturbance showing association with increased dose even within the lowest dose range (0-7.5mg daily dose prednisolone). Prednisolone use has been associated with increased fatigue levels in a cross-sectional study of 1,197 members of the German Sarcoidosis Society (mean difference in FAS score 1.6, $p<0.001$), as was methotrexate (mean difference in FAS score 3.8, $p=0.006$) and the use of two or more medications for sarcoidosis (mean difference in FAS score 2.1, $p=0.037$), although these were not adjusted for disease severity and may reflect more severe disease (152). A prospective study of 51 new cases of pulmonary sarcoidosis measured fatigue scores before and immediately after a six-month course of oral corticosteroids; of these, nine cases (17.6%) showed clinically important worsening in fatigue scores post-treatment, although it should be noted that patients had already discontinued steroids by the time of their post-treatment measurements, making it impossible to determine what happened to fatigue scores whilst receiving corticosteroids (88).

Measuring Fatigue in Sarcoidosis

The fatigue experienced by patients with sarcoidosis has been shown to vary between patients, with different natures of fatigue identified. In a survey of 434 outpatients with sarcoidosis in Maastricht three distinct types of fatigue experienced by patients were discovered; *mild fatigue*, where the fatigue was not severe enough to render a complaint on daily life; *intermittent fatigue*, where the severity of fatigue varied throughout the day; and *all-day fatigue*, where sufferers

felt tired throughout the day (134). Furthermore, the presence of all-day fatigue correlate with higher levels of depressive symptoms and anxiety, impacting more on daily quality of life (142). Defining fatigue is therefore difficult and requires an appropriate choice of instrument.

WASOG strongly recommends that all clinical trials involving patients with sarcoidosis should include measures of quality of life, including fatigue, as part of the outcomes assessed (166), reflecting both the frequency with which this symptom occurs and the impact that it has. Accuracy in measuring fatigue is challenging due to a complex interaction of multiple factors, including biological processes, psychosocial difficulty and behavioural manifestations (109). Multiple questionnaires have been designed and validated for measuring fatigue but a preference for an endpoint that incorporates "validated, disease-specific objective instruments" is suggested by WASOG for measuring fatigue in sarcoidosis populations (166).

A list of potential "objective instruments" that measure fatigue in sarcoidosis patients has been created by WASOG in their recommendations for endpoint in clinical trials involving patients with sarcoidosis (166). The possible questionnaires, including ones previously used as outcome measures for fatigue in studies involving patients with sarcoidosis, are described in detail below. It has been acknowledged that in view of the difficulties of characterising fatigue, as well as no single instrument being a perfect disease-specific measure, trials investigating change in fatigue should use several complementary questionnaires. This may include a specific questionnaire evaluating fatigue symptoms, such as FAS, alongside a general quality of life scale such as the Short-Form 36 (SF-36) instrument and measurement of confounders including depression (166). An extended summary of possible tools for monitoring fatigue, identified from previous observational or interventional studies investigating fatigue in patients with sarcoidosis, is shown below in table 5.

***Table 5** – Summary of suggested fatigue-specific outcome measures previously studied in sarcoidosis cohorts or used in trials investigating sarcoidosis-associated fatigue*

Questionnaire	Properties studied in sarcoidosis populations?	Used in sarcoidosis intervention trial?	Specific for fatigue?	MCID specified	Severity/ clinically relevant cut-points identified?
FAS	✓	✓	✓	✓	✓
FACIT-Fatigue	X	✓	✓	✓*	X
MFI-20	✓	X	✓	✓*	✓*
FSS	X	✓	✓	✓*	X
CIS (Fatigue subscale)	X	✓	✓	X	✓*

*Established in conditions other than sarcoidosis

Fatigue Assessment Scale (FAS)

The FAS questionnaire is a widely-used tool for measuring fatigue in sarcoidosis which was originally developed to measure fatigue within a Dutch working population. It contains ten questions, five reflecting mental fatigue and five reflecting physical fatigue, with each question scored between 1 and 5, with 5 corresponding to worst possible fatigue. Patients can score a maximum of 50 points and a minimum of 10 points, with a score of 22 or more indicating the presence of significant fatigue (112); a sub-group of “extreme fatigue” is denoted by scores of more than 34 points. The measurement of fatigue has been shown to be independent of depressive symptoms (167).

The tool was subsequently tested within a cohort of 1,126 patients with sarcoidosis in the Netherlands, with 246 participants repeating the measurement after seven days, to validate its use for measuring fatigue in sarcoidosis (112). Content validity, construct validity and internal consistency were all good, and a test-retest reliability of 0.89 was found within the group repeating the measurement. Overall, the tool was found to be useful for measuring fatigue in patients with sarcoidosis, leading to its validation in sarcoidosis cohorts in other countries (168) and subsequent use in

exploring fatigue levels reported by patients with sarcoidosis in the USA (113), Poland (169) and the UK (170). Moreover, the minimal clinically important difference (MCID) for patients with sarcoidosis has been identified as a 4-point change; this was estimated through anchor-based and distribution-based methods, using data from 321 patients at Maastrict University Medical Centre (171).

One potential problem of the FAS questionnaire is items 4 and 10 ("I have enough energy for everyday life" and "When I am doing something, I can concentrate quite well"), require negative scoring. This leads to confusion in participants completing the questionnaire, and has been suggested as a cause of reduced internal consistency. In one study of 107 patients with sarcoidosis attending an American outpatient pulmonary clinic, FAS scores were measured, with items 4 and 10 subsequently removed to compare the internal consistency. Initial internal consistency of the FAS using Cronbach's alpha was 0.740, indicating acceptable internal consistency, but this increased to 0.911 (excellent consistency) after removal of items 4 and 10 (172). Previous work within the sarcoidosis patient cohort in Norwich did not replicate this finding; internal consistency of the FAS from 66 patients within a previous study was 0.913 with all items included and 0.921 with items 4 and 10 removed (unpublished data from previous trial (170)), showing excellent internal consistency as measured by Cronbach's alpha. This discrepancy may be explained by the different settings where the questionnaires were completed. In the Norwich study, participants had the questionnaire explained to them by a member of the research team, including the reverse marked items. In the American study participants completed the questionnaire in an outpatient setting where they may not have received instruction.

Despite this potential negative of the FAS, the body of evidence for using this questionnaire in patients with sarcoidosis, as well as a defined cut-off for significant fatigue and a defined MCID mean that the FAS has a number of benefits and has been used in previous trials where fatigue has been an outcome measure (173, 174).

Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue)

The FACIT-Fatigue questionnaire was initially developed to measure fatigue in cancer patients using computerised adaptive testing to identify questions that provided the most information about patient-reported fatigue from a larger existing questionnaire. Two groups of respondents completed the questionnaire; 1010 members of the general population and 1022 patients with various cancers, leading to the development of the final 13-item questionnaire (175). Each item is marked between 0 and 4 to give a maximum score of 52 points, with higher scores indicating worse fatigue. As with the FAS questionnaire, two items ("I have energy" and "I am able to do my usual activities") are reverse scored.

The tool has been used in patient groups with cancer, rheumatoid arthritis and systemic lupus erythematosus to determine the MCID, which has been estimated through multiple methods to be between 3 and 6 points, although this was validated in cohorts of patients with rheumatoid arthritis, cancer and systemic lupus erythematosus (176). No cut-off has been described for severity of fatigue with this scale. It has been used previously in two trials investigating possible treatments for sarcoidosis-associated fatigue, where changes in the FACIT-Fatigue score were similar to those seen in the FAS score but appeared to occur earlier in treatment (173, 174).

Multidimensional Fatigue Inventory (MFI-20)

The MFI is a 20-item questionnaire that was designed to be self-completed by patients. The questionnaire covers five dimensions; general, mental and physical fatigue as well as reduced motivation and reduced activity. Each of the items is scored out of five, giving a potential score range of 20-100 points. It was initially validated in cancer patients who had been treated with radiotherapy, as well as healthy populations (students, junior physicians and army recruits) in the Netherlands, and has good construct validity and internal consistency (177). Subsequent studies investigating the use of the MFI-20 estimated a MCID of between 11.5 and 13.3 points (176). Using data from cancer patients a cut-off score

of 53 points has been determined as the threshold for significant fatigue (178), although the validity of this cut-point in patients with sarcoidosis has not been performed.

The MFI questionnaire has been studied in sarcoidosis populations. One study administered the questionnaire to 1197 patients in Germany, showing that the MFI-20 showed similar percentages of patients reporting fatigue using the 53-point cut-off compared with the FAS questionnaire. Sixty-eight percent of the population exceeded the MFI-20 fatigue cut-off compared with seventy percent exceeding the FAS fatigue cut-off. The total scores for the two questionnaires were also strongly correlated (r=0.86) (179), indicating that the MFI performs similarly to the FAS questionnaire in patients with sarcoidosis.

Fatigue Severity Scale (FSS)

The Fatigue Severity Scale was first used in 1989, initially in patients with multiple sclerosis (MS) and SLE, as well as healthy volunteers (180). It is a nine-item short questionnaire, with each item scored between 1 and 7 points and the overall score averaged to give a total score between 1 and 9. Alternatively the individual question scores can be added to give a score out of 63; a score of 36 or more indicates marked fatigue. When using the averaged value, the MCID has been estimated as 1 point from studies of patients with rheumatoid arthritis, lupus and multiple sclerosis (176), although no studies have investigated the properties of the scale in patients with sarcoidosis. In other conditions the FSS has been found to be internally consistent and correlated with visual analogue measures of fatigue (180). The FSS has only been used in one study including patients with sarcoidosis; this was an interventional trial investigating the effects of a structured exercise program on quality of life where change in fatigue was a secondary outcome (181).

Checklist Individual Strength (CIS) Fatigue subscale

The CIS was initially developed in 1994 to measure fatigue in patients with chronic fatigue syndrome (182). The original questionnaire consisted of 20 items (CIS20R), though a subscale of 8 items relating to 'subjective fatigue' (CIS fatigue subscale; CIS8R) can be used separately to measure fatigue. CIS8R consists of 8 items, and has identified cut-offs for fatigue severity; 27-35 points for increased fatigue and >35 points for severe fatigue, although these cut-points have been identified from patients with rheumatoid arthritis, not sarcoidosis (183). No MCID is reported for this tool. The CIS8R has been shown to have good internal consistency (Cronbach's alpha 0.92) and criterion validity (correlation co-efficient (r) of 0.61 compared with a fatigue visual analogue scale), although these values were from populations with rheumatoid arthritis (184). In sarcoidosis, only the fatigue subscale of the CIS (CIS8R) has been used previously (185).

Impact of sarcoidosis-associated fatigue

Impact upon health-related quality of life

Quality of life is distinct from health-related quality of life (HRQoL), although distinguishing between the terms can be difficult. Quality of life is a concept which encompasses all aspects of life and is difficult to measure, requiring psychological, social and economic wellbeing to be considered alongside direct health-related effects of both disease and treatment. Regarding the term "Quality of Life" in medical literature, it may not have a defined meaning and is frequently substituted for HRQoL (186). By contrast, HRQoL is more narrowly-defined as it focuses on the health or disease status of an individual and how this influences quality of life, although this itself can be defined in multiple ways including the frequently used term "health state" (187).

The presence of fatigue has been shown to have a negative impact on HRQoL (122). By comparison, traditional measures of disease severity including spirometric values (188) and chest X-ray staging are not associated with measures of health-

related quality of life in patients with sarcoidosis (189). Multiple studies have measured fatigue and quality of life in patients with sarcoidosis. A search of the Medline electronic database, using the terms *"sarcoid" OR "sarcoidosis" OR sarcoidosis [MeSH Terms] OR Sarcoid* (truncation)* ***AND*** *quality of life* ***AND*** *fatigue*, identified a number of studies that have measured fatigue and quality of life in patients with sarcoidosis (Table 6). Common findings across the globe demonstrate that the presence of fatigue negatively affects quality of life in patients with sarcoidosis.

A variety of quality of life measures have been used, as has a variety of fatigue scales. In each case a negative relationship between fatigue and quality of life has been found, with one exception where a single questionnaire was used to measure both fatigue and general quality of life (190).

Table 6 *– Studies investigating links with quality of life in sarcoidosis*

Source	Country	No. Patients	Fatigue Measure	QoL measure	Findings
Michielsen et al (189)	Croatia	145	FAS	WHOQOL-100	Fatigue adversely affects all QoL domains
Spruit et al (188)	Belgium	22	CRDQ Fatigue Domain	SF-36	Fatigue correlates with SF-36 scores
Elfferich et al (144)	Netherlands	441	FAS	WHOQOL-BREF	Fatigue and depressive symptoms predict QoL
Korenromp et al (145)	Netherlands	75	CIS (fatigue severity subscale)	SF-36	Fatigued patients scored significantly lower in all domains of SF36
Wirnsberger et al (190)	Netherlands	71	WHOQOL-100 (fatigue facet)	WHOQOL-100	No correlation between fatigue facet and psychological health
Jastrzebski et al (191)	Not stated	111	FAS	SF-36	Fatigue correlated with quality of life in SF-36

CIS = Checklist Individual Strength, CRDQ = Chronic Respiratory Disease Questionnaire, FAS = Fatigue Assessment Scale, SF-36 = Short Form 36, WHOQOL-100 = World Health Organisation Quality of Life Scale - 100, WHOQOL-BREF = World Health Organisation Quality of Life Scale – Brief

Impact of fatigue upon physical capacity

Exercise limitation is a common problem in sarcoidosis, with multiple factors potentially responsible for exercise intolerance. These may include peripheral muscle weakness due to direct involvement of sarcoidosis, resulting from corticosteroid treatment, reduced pulmonary function and cardio-respiratory reserve, or general deconditioning (192). One study performed cardiopulmonary exercise testing of patients with thoracic sarcoidosis, revealing that these patients have reduced pulmonary gas exchange, even in some cases where transfer factor is normal (193).

However, a direct relationship between fatigue and exercise capacity measured in a laboratory environment has not yet been proven. A study of 124 patients with sarcoidosis revealed that although 45% of patients had reduced exercise capacity measured by the six-minute walk test (6MWT), there was a non-significant difference in the number of patients with reduced 6MWT seen between fatigued and non-fatigued patients. More than half of the patients in this study reporting fatigue had no reduction in exercise capacity (194). Later analysis of the same cohort in a subsequent study showed a relationship with quality of life, as well as a relationship between fatigue score (measured by FAS) and quality of life, although it should be noted that only 19% of variability in the quality of life score (measured by the WHOQOL-BREF) was explained by the changes in FAS and 6MWT values (195).

The 6MWT, as a self-paced test, measures the submaximal level of functional capacity (196). Other laboratory measures are incremental and measure maximal functional capacity. One example is the steep ramp test (SRT), a cycle-ergometer test with incremental load which gives results highly comparable with full cardio-pulmonary exercise test (CPET) results. In an evaluation of 147 patients with sarcoidosis undergoing both 6MWT and SRT, neither the oxygen uptake during SRT, maximal work during SRT, distance covered during 6MWT, or percentage predicted 6MWT distance showed significant correlation with FAS scores (r= -0.24, -0.27, -0.27 and -0.25 respectively) (197). Even full CPET testing has not shown an association with fatigue; a study of 160 sarcoidosis cases revealed no association

between oxygen exchange at maximal exercise and fatigue scores (r = -0.060, p=0.474), although maximal work performed by subjects was not reported and so the link between fatigue and effort cannot be commented upon (193). Another study including 22 patients with sarcoidosis found no relationship between fatigue measured by the MFI-20 questionnaire and peak oxygen consumption (VO_2max) calculated during an incremental CPET on a treadmill (124). These results reinforce the variable impact of fatigue upon physical capacity in laboratory settings.

Impact of fatigue upon daily activity

In contrast to laboratory measures of exercise capacity, such as the 6MWT and SRT, physical activity in free-living refers to the amount of exercise or activity performed by a person in their own environment. According to the *International Classification of Functioning* defined by the Wold Health Organization (WHO), activity (or exercise) capacity refers to "an individual's ability to execute a task or action… indicating the highest probable level of functioning" whereas exercise performance "describes what an individual does in his or her current environment" (198). Whilst the former is typically assessed in a controlled environment using a standardised method, the latter is context specific and impacted by environmental and personal factors.

Measuring physical performance in free-living conditions is more challenging than measuring physical capacity. Methods of accurately measuring energy expenditure, such as double-labelled water, are well validated but expensive (199). Furthermore, these methods measure energy expenditure in free-living conditions, rather than patterns of physical activity (200). Questionnaires are a simple method of recording physical activity in research participants but are open to recall bias and have been shown to be a poor method of assessing activity. In the case of the International Physical Activity Questionnaire – Short Form (IPAQ-SF), a widely used activity questionnaire, the questionnaire overestimated physical activity by an average of 84 percent compared with objective measures of activity according to one systematic review (201). New accelerometer-based devices can measure

movements and track activity patterns. These devices have been shown to be able to reliably measure physical activity in free living conditions (202) and are used in large-scale population studies such as the National Health and Nutrition Examination Survey (NHANES) in the United States (203) and the UK Biobank study (204) as objective measures of physical activity.

In sarcoidosis, two studies have investigated activity patterns in patients with fatigue. The first study, from Korenromp and colleagues, measured fatigue levels in 75 patients with sarcoidosis as well as measuring daily activity over a seven day period using an ankle-worn tri-axial accelerometer (145). Levels of activity, measured by "accelerations" recorded by the device, were lower in the fatigued group compared with the non-fatigued group on both weekdays (75.14+/-24.09 accelerations/day vs 82.06+/-27.69 accelerations/day, p=0.001) and weekend days (66.93+/-29.43 accelerations/day vs 79.81+/-31.99 accelerations/day, p<0.001). Unfortunately, no measure of physical capacity was undertaken so it was not possible to determine if a relationship existed between exercise performance and exercise capacity.

A more recent study by Bahmer and colleagues investigated the association between activity levels measured by the sensewear armband (BodyMedia Inc, Pittsburgh PA, USA), a tri-axial accelerometer with in-built galvanometer and the ability to measure metabolic activity, and fatigue measurements (205). The study also included measurements of physical capacity (6MWT), generic and health-related quality of life, and pulmonary function tests. The results showed only a weak association between fatigue scores, from the "reduced activity" and "physical activity" subscales of the MFI-20 questionnaire, and daily step-count calculated from the sensewear armband, with correlations co-efficients of -0.277 and -0.274 respectively (p=0.037 and 0.039). The total MFI-20 score had weaker correlation with daily step count, and did not show a statistically significant association (r=-0.259, p=0.052). In contrast, exercise capacity (6MWT) showed a stronger correlation with steps per day (r=0.499, p<0.001), remaining significant within a multiple regression model for predicting daily step count alongside St George's respiratory questionnaire score and short form 12 (SF-12) physical health score (r^2 =

0.34, p=0.002). In contrast to the earlier study by Korenromp et al (145), fatigue was not found to be a significant predictor of daily activity. This may be due to a number of factors. Firstly, step-count may not be the ideal measurement of physical activity as it does not consider the intensity of activity (e.g. metabolic activity), which may be reduced in fatigue. The authors also discuss further possible causes for the lack of association, notably the small number of participants, the large number of non-fatigued patients, and the lack of a disease-specific quality of life score such as the Kings' Sarcoidosis Questionnaire.

The conflicting results from the two studies, as well as the shortcomings in design and outcome measures, means that there is not yet evidence to prove or disprove a significant association between daily physical activity and sarcoidosis-associated fatigue. Furthermore, whether exercise in free-living is altered through purely physical limitations, or due to mental aspects of fatigue seen in sarcoidosis (170) impacting upon volition, is as yet unclear.

1.10 Rationale and Overview of this Thesis

Fatigue is a frequent manifestation of sarcoidosis that can be debilitating for patients and difficult to treat for the physician. Limited options are available if fatigue persists despite standard treatment, or where fatigue is the only symptom and systemic therapies are not recommended or patients do not wish to receive systemic treatments such as corticosteroids. The use of symptom-targeted therapies, including neurostimulants, offers a possible treatment option directly targeting the symptom of fatigue. The use of such agents requires evaluation, both in terms of efficacy and safety, but questions about the ideal trial design to answer these clinical questions exist. The aim of this thesis is to determine if it is possible to perform a randomised-controlled trial powered to confirm a clinical effect for neurostimulants in sarcoidosis-associated fatigue.

The first chapter within this thesis presents a systematic review of the existing evidence for all possible treatments of fatigue in patients with sarcoidosis, including both pharmacological and non-pharmacological treatments (**chapter 2**).

The next chapter presents a crossover study comparing two widely used accelerometer-based activity monitors, which helps to determine the preferred device for patients in future trials, as well as comparing participants' activity levels with recorded fatigue scores (**chapter 3**).

In **chapter 4** and **chapter 5**, the feasibility study *"Fatigue and Sarcoidosis – Treatment with Methylphenidate (FaST-MP)"* investigates how best to design a full phase-III study of neurostimulant medication for sarcoidosis-associated fatigue. It aims to determine the number of participants within a single centre who would be eligible for such a study, as well as the number who agree to participate. The study design allows longer follow-up of patients receiving methylphenidate than has previously been performed; this allows estimation of the persistence of treatment effect between placebo and medication arms. Following this, **chapter 6** reports the outcomes of focus group discussions with participants from the *FaST-MP*, describing the experience of participants within *the FaST*-MP study and what might be done in a future trial which might improve the experience for participants.

Chapter 7 reports the results of a questionnaire study comparing commonly used questionnaires in patients with sarcoidosis, including how measures of severity, treatment, and patient-reported fatigue and depression symptoms affect quality of life scores. The results from this will further support decisions regarding future trial design through helping to determine the preferred questionnaires for patient-reported outcomes and quality of life.

The overall results from the studies within this project are discussed in **chapter 8**, including the potential design of a subsequent phase III study investigating the clinical efficacy of neurostimulants for the treatment of sarcoidosis-associated fatigue. These discussions include the challenges posed to any future study, identified from those encountered within the *FaST-MP* study.

Chapter 2: *Management of sarcoidosis-associated fatigue – a systematic review of evidence for treatment*

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2.1 Introduction

In the first chapter of this thesis the potential causes for developing marked fatigue in patients with sarcoidosis were discussed. Sarcoidosis-associated fatigue may be multifactorial and related to co-existent reversible conditions such as obstructive sleep apnoea; it is important that these conditions are excluded or managed in the first instance. Once these conditions have been excluded or treated, consideration can be given to management strategies aimed at directly treating the symptoms of fatigue. A systematic review of the literature was undertaken to evaluate the evidence for management strategies that have a potential role in the management of sarcoidosis-associated fatigue; the results are presented within this chapter.

Background

Both pharmacological and non-pharmacological interventions have been suggested for the treatment of fatigue in patients with sarcoidosis. Corticosteroids are the most commonly prescribed medication for treatment of sarcoidosis, although they have the potential to cause side effects which include fatigue. However, few studies have investigated fatigue during and after receiving corticosteroids. Treatment of the underlying inflammatory cascade hypothesised to drive symptoms of fatigue has been trialled. Blockade of the action of TNF-alpha, which is released by alveolar macrophages and is involved in the initial pathogenesis of sarcoidosis (206), has been investigated as a treatment for refractory sarcoidosis. Amongst trials investigating these agents, measurements of fatigue pre- and post-treatment have been taken. A novel therapy, ARA 290 (207), a small peptide modelled on erythropoietin and which possesses anti-inflammatory activity, has also been investigated for its potential effects on symptoms of small-fibre neuropathy. These symptoms include cognitive failure and fatigue (208).

Direct, symptomatic treatment of fatigue has been trialled using neurostimulant therapy in other conditions where fatigue is a common and debilitating symptom. Methylphenidate and dexmethylphenidate, the d-isomer of methylphenidate and approximately twice as potent as a result, are central nervous system stimulants of

the piperidine and phenethylamine classes which act by inhibiting noradrenergic and dopaminergic transport within certain areas of the brain (209). Methylphenidate is widely prescribed for its use in attention-deficit hyperactivity disorder (ADHD) (210), both in children and adults, but has been also trialled as treatment for fatigue in other situations (including chemotherapy (211), post-radiotherapy (212), HIV (213), and Parkinson's disease (214)) with some benefit. Another neurostimulant, Modafinil, and its enantiomer armodafinil, are used for promoting wakefulness in narcolepsy. They have a complex profile of neurochemical actions, not all of which are fully understood, with the overall effect being different to those of amphetamines (215).

Finally, physical activity programmes have been shown to have wide-reaching benefits. The most widely-known example of this is the effect of pulmonary rehabilitation in chronic obstructive pulmonary disease (COPD), which includes improving dyspnoea scores, health-related quality of life, anxiety and depression (216). The use of pulmonary rehabilitation in patients with interstitial lung diseases is recommended by international guidelines (83, 217); the magnitude of benefit in these patients is similar to that seen in COPD patients (218). There have been recent trials investigating the use of physical activity and rehabilitation programmes in patients with sarcoidosis; among the outcome measures these trials investigated the impact of physical activity programmes on fatigue.

This systematic review aimed to examine the existing evidence for possible interventions which may affect fatigue in patients with sarcoidosis who are experiencing clinically significant fatigue. This includes assessment of the quality of the evidence, including current shortcomings, and to present the results as a narrative review of the available data.

2.2 Methods

Publication Search

This systematic review was registered with PROSPERO (registration number CRD42015030079) and was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (219). The full protocol of the methodology for the review can be accessed online through the PROSPERO database using the registration number. The electronic databases Medline (using PubMed) and Web of Science were searched using the following search strategy: *"sarcoid" OR "sarcoidosis" OR sarcoidosis [MeSH Terms] OR Sarcoid* (truncation)* ***AND*** *"fatigue" OR "chronic fatigue" OR "chronic fatigue syndrome" OR fatigue [MeSH Terms] OR fatigue syndrome, chronic [MeSH Terms]* ***AND*** *"treatment" OR "management" OR "clinical trial".*

Bibliographies of appropriate papers were reviewed for relevant additional sources. The title and abstract of all these papers were reviewed for relevance, with irrelevant studies excluded. Remaining papers were acquired and reviewed in full. The initial search included trials published up to December 2015. An updated search was performed in May 2018 to identify any new studies published.

Selection Criteria

Studies were considered suitable for inclusion if they evaluated the effect of an intervention (either pharmacological or non-pharmacological) on fatigue in patients with sarcoidosis. All trial designs (case series, case-control, cross-over and parallel-arm randomised controlled trials) were included in the qualitative synthesis; only case reports were excluded, meaning trials where no comparator group or comparator intervention were included. This ensured the broadest collection of evidence. The studies must have 1) evaluated sarcoidosis patients exclusively or presented results of the patients with sarcoidosis separately to those of other conditions if multiple disease cohorts were included in the same study, 2) evaluated the efficacy of the intervention on a measured score of fatigue, 3) reported quantitative results for changes in fatigue score between pre- and post-intervention results and 4) be in English and presented in full-text form.

Data Collection

Data extraction was performed independently by two assessors. Dr Chris Atkins and Professor Andrew Wilson extracted information using a pre-determined checklist. In addition, the Cochrane Collaboration's tool for assessing risk of bias (220) was also used to assess the methodological quality of each trial, enabling identification of possible sources of bias at a study level. From each paper the following data was collected: Main author's last name, year of publication, study design, number of participants, severity of sarcoidosis in participants by CXR staging (Scadding score, if given), intervention (including dose regime and duration of intervention), measurement score of fatigue used, change in fatigue outcome, number of participants reaching minimum clinically important difference on outcome score (if given), number of participants completing the intervention and adverse events reported within the trial. The summary measure of interest was mean improvement of fatigue score. Due to the small number of studies available for inclusion, and the heterogeneity of interventions and study designs, a meta-analysis of data was not possible. A narrative review of the data is presented for all the available data.

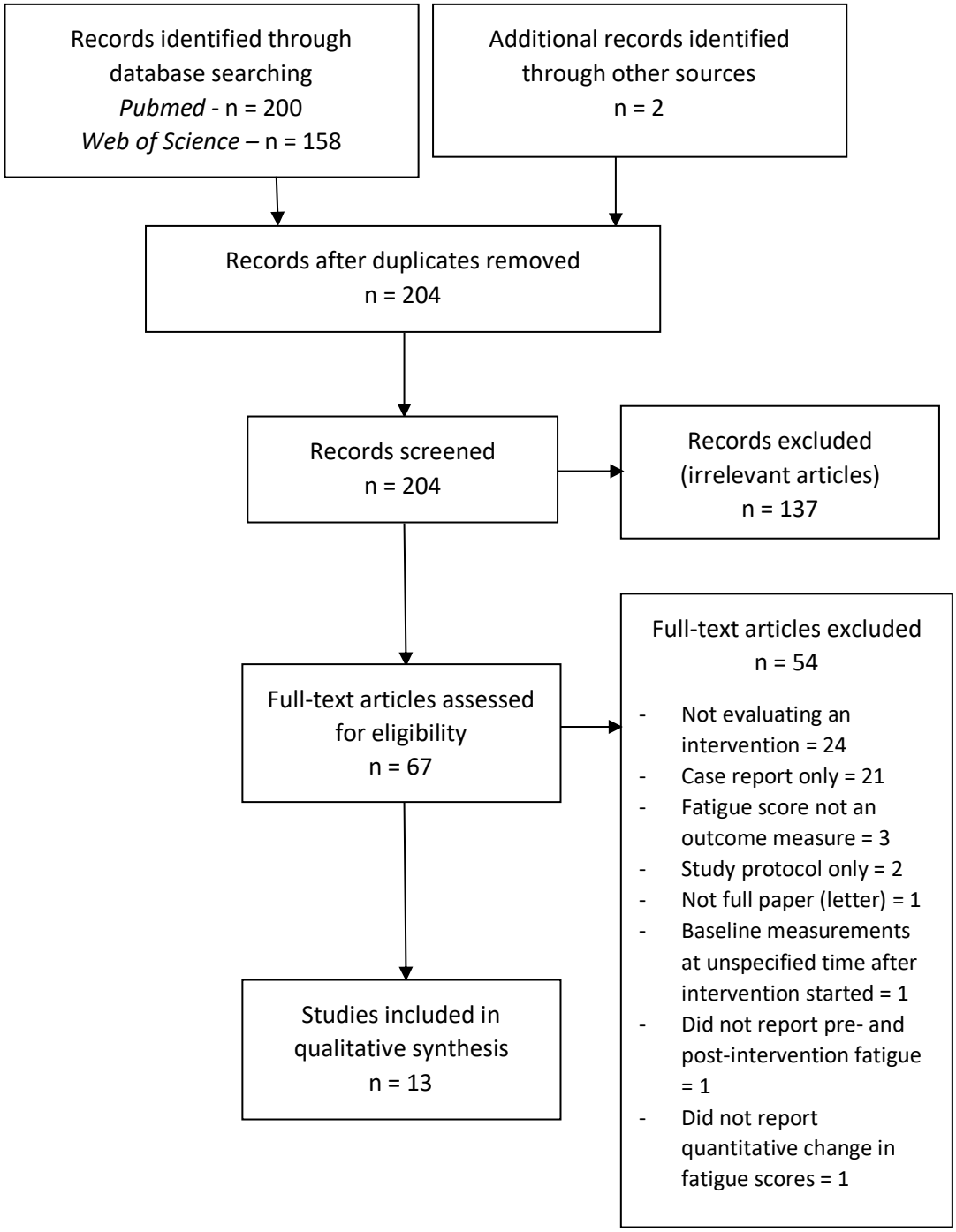
2.3 Results

Search results and characteristics of eligible trials

The initial search was undertaken in November 2015 and published in 2016 (221). Through the planned search strategy, 150 records were identified from Medline and 126 records from Web of Science. Two further papers of interest were identified through review of the bibliographies of the identified papers. A total of 154 papers were identified from the initial search after duplicates were removed. An updated search in May 2018 identified 200 records from Medline and 158 records from Web of Science; this included a total of 50 extra papers of interest (204 in total) compared with the initial search once duplicates were removed. Titles and abstracts were reviewed for relevance. Studies were excluded if they did not include patients with sarcoidosis, were not evaluating a potential intervention to

treat fatigue or were case reports; review articles were also excluded but reviewed for other relevant papers of interest. From the screened papers, 67 studies were identified, of which thirteen met full the criteria for inclusion. The flow diagram (PRISMA 2009) of screened articles is shown in Figure 3. Only six randomised controlled trials (either parallel arm or cross-over) were identified, one of which randomised between two doses of the same drug without a comparator intervention or placebo. Of the remaining articles, six were observational studies and one was a retrospective review of cases.

Figure 3 *– Flow diagram of study identification and exclusion*



Six papers evaluated formal physical activity programs (five supervised exercise programmes, one inspiratory muscles training programme), two evaluated systemic treatment with tumour necrosis factor alpha (TNF-alpha) inhibitors (infliximab and adalimumab), two evaluated symptom-targeted therapy with neurostimulants (dexmethylphenidate and armodafinil), one trial reviewed change in fatigue after receiving prednisolone, one trial investigated a novel molecule aimed at treating small-fibre neuropathy (ARA 290) and one trial investigated the use of repository corticotropin (RCI) in patients receiving long-term prednisolone. All but three trials chose the FAS as a measure of fatigue. Of the remaining studies, two used the FSS and one used the CIS Fatigue subscale. The properties of these questionnaires are discussed in Chapter 1, section 1.9.

Across all the included studies, a total of 602 patients were included across all the trials, with 296 participants in one study (222). The details of each included studies are shown in Table 7 for pharmacological interventions and Table 8 for non-pharmacological interventions, with the risk of bias within each study displayed in Tables 9 and 10 for pharmacological and non-pharmacological interventions respectively. Furthermore, in addition to the thirteen studies that met the inclusion criteria, three papers that did not meet the inclusion criteria but provided useful information are discussed.

Table 7 *- Overview of trials including change in fatigue as an outcome measure (Pharmacological interventions)*

Author and Year	***Lower et al. 2007 (173)***	***Erckens et al. 2011 (105)***	***Heij et al. 2012 (207)***	***Van Rijswijk et al. 2013 (185)***	***Lower et al. 2013 (174)***	***Aggarwal et al. 2016 (223)***	***Baughman et al. 2017 (224)***
Study Design	Cross-over RCT	Observational study	RCT	Retrospective case review	Cross-over RCT	Observational study	Parallel Arm RCT
Intervention	Dex-methylphenidate	Adalimumab	ARA 290	Infliximab	Armodafinil	Prednisolone	Repository Corticotropin Injection (RCI)
Dose	Up to 10mg twice daily	40mg S/C weekly	2mg IV weekly	5mg/kg IV at 0,2,6,10,14 and 18 weeks	Up to 250mg twice daily	0.75mg/kg for 1 month *then* wean to zero over 6 months	80 units twice weekly
Comparator	Placebo	None	Placebo	None	Placebo	None	RCI, 40 units twice weekly
Duration	8 weeks per arm	12 months	4 weeks	18 weeks	8 weeks per arm	6 months	24 weeks
No. participants	10	26	22 (10 placebo)	27‡	15	51	18 (16 analysed)
% Male	20%	36.6%	50%	60%	33.3%	54.9%	26.9%
Age (mean ± SD)	52 (range 39-74)	51 ± 15	48.1 ± 2.7	48.9 ± 10.1	54 (range 35-62)	Not stated	58.5 (range 35-68)
Disease stage (0/I/II/III/IV)	Not stated	16/4/4/2/0	Not stated	5/7/14/5/14	3/5/2/2/3	0/32/19/0/0	Not specified
Measurement of fatigue	FAS and FACIT-Fatigue	FAS	FAS	'Fatigue severity' within CIS	FAS and FACIT-Fatigue	FAS	FAS
INTERVENTION: Pre- and Post-fatigue scores (mean ± S.D. unless stated)	**FAS** (range)**:** Pre: 32.5 (9-44) Post: 27.5 (23-43) **FACIT-F** (range)**:** Pre: 19.5 (13-48) Post: 29.5 (5-50)	Pre: 31.1 ± 11.1 Post: 28.9 ± 10.0	Pre: 37.9 ± 2.6 Post: 33.3 ± 2.8	Pre: 49.4 ± 9.2 Change: -5.3 ± 8.5	**FAS** (range)**:** Pre: 37 (14-43) Change: -4.5 (-20, 5) **FACIT-F** (range)**:** Pre: 23 (10-47) Change: +9(-12,26)	Pre (median): 24 (range 19-30) Post (median): 21 (range 17-27)	Pre: 28 (range 15-46) Week 7: 26 (range 10-37) Week 24: 22 (range 11-42)

Author and Year	*Lower et al. 2007 (173)*	*Erckens et al. 2011 (105)*	*Heij et al. 2012 (207)*	*Van Rijswijk et al. 2013 (185)*	*Lower et al. 2013 (174)*	*Aggarwal et al. 2016 (223)*	*Baughman et al. 2017 (224)*
COMPARATOR: Pre- and Post-fatigue scores (mean ± S.D. unless stated)	Average scores in placebo arm†: **FAS**: 33.6±4.43 **FACIT-Fatigue**: 24.3± 5.41	N/A	Pre: 33.6 ± 2.3 Post: 29.8 ± 3.3	N/A	**FAS** (range)**:** Pre: 37 (14-43) Change: +3.5 (-9,14) **FACIT-Fatigue** (range)**:** Pre: 23 (10-47) Change: -5 (-17,11)	N/A	*Not analysed separately: results above included all patients receiving RCI regardless of dose*
Statistical difference vs. comparator	**FAS**: p=0.0295 **FACIT-Fatigue**: p=0.0040 (between groups)	P < 0.01 compared with baseline	Non-significant between groups	P=0.003 compared with baseline	**FAS**: p=0.0295 **FACIT-Fatigue**: p=0.0040 (between groups)	P=0.004 compared with baseline	Not performed
Number of participants with clinically significant improvement	Not stated	Not clear; 14/21 less fatigued but doesn't state MCID used.	Not stated	Not stated	64% treated with armodafinil improved FAS by 4 points (MCID); only 7% in placebo	21 (63.6% of initially fatigued patients)	Ten patients had met FAS MCID of 4 points reduction or more); eight patients had met MCID at 24 weeks.
Drop outs/ Side Effects	No withdrawals 4 patients required lower afternoon dose	No withdrawals. 1 severe injection site reaction	No drop outs	3 patients discontinued within 6 infusions: 1) Allergic reaction 2) Progression of dyspnoea 3) Hepatitis (due to methotrexate)	1 withdrawal due to severe anxiety	Not stated	One patient withdrew pre-therapy; one patient withdrew because of toxicity. Seven patients received reduced dosage.
Evidence of treatment effect in fatigue	Yes	Yes	No	Yes	Yes	Yes (new diagnoses only)	Yes, although no placebo arm to compare against

†Group values at the end of the placebo phase not given, data only presented as average values across placebo phase.

‡48 patients included in study but quality of life scores (including fatigue) only available in 27.

FAS = Fatigue Assessment Scale; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy – Fatigue; MCID = Minimal Clinically Important Difference

Table 8 *- Overview of trials including change in fatigue as an outcome measure (Physical exercise interventions)*

Author and Year	***Strookappe et al. 2015 (225)***	***Marcellis et al. 2015 (226)***	***Strookappe et al. 2015 (227)***	***Karadalli et al. 2016 (228)***	***Lingner et al. 2018 (222)***	***Naz et al. 2018 (181)***
Study Design	Observational Study	Observational Study	Retrospective, Observational	Parallel Arm RCT	Observational study	RCT
Intervention	Physical activity programme	Physical activity programme	Physical activity programme	Inspiratory muscle training programme	Physical activity programme	Physical activity programme
Dose	12-week physical activity programme	13-week physical activity programme	12-week physical activity programme	30 minutes/day	3-week intense activity and rehab programme	12-week physical activity programme
Comparator	None	None	41 patients who chose not to participate in programme	Sham training	None	Usual Care
Duration	12 weeks	13 weeks	12 weeks	6 weeks	3 weeks	12 weeks
No. participants	12	24	49	34 (30 analysed)	296	18
% Male	91.7%	75%	57.1%	36.6%	53.0%	33.3%
Age (mean ± SD)	53.2 ± 11.7	49.4 ± 10.5	47.6 ± 11.3	Intervention: 45.1 ± 8.1 Control: 47.5 ± 12.9	49.1 ± 9.7	Intervention: 59 (52-64) Control: 51 (45-57)
Disease stage (0/I/II/III/IV)	0/0/0/0/12	0-I = 29.2% II-III = 66.6% IV = 4.2%	4/11/22/0/4	Stage I = 9 subjects (30%) Stage II = 21 Subjects (70%)	0 = 1.5% I = 18.3% II = 58.0% III = 13.7% IV = 4.6%	0/0/0/10/8
Measurement of fatigue	FAS	FAS	FAS	FSS (Turkish version)	FAS	FSS (Turkish version)
INTERVENTION: Pre- and Post-fatigue scores (mean ± S.D. unless stated)	Pre: 28.5 ± 5.4 Post: 27.7 ± 5.7 (6 of the 12 patients had FAS >21 at baseline)	Pre: 29.7 ± 7.7 Post: 27.0 ± 7.3 (in 18 patients completing course)	Pre: 29.8 ± 8.1 Post: 25.6 ± 7.5	Pre: 39.2 ± 14.9 Post: 31.4 ± 15.0 Mean difference: -8.0 (-14.4 to -2.0)	Pre: 26.6 ± 7.7 Mean difference post-intervention: -4.09 (95% C.I. -4.82, -3.36)	Pre (median): 40 (range 23-47) Median change in FSS: -7 points (range -10 to +2)

Author and Year	*Strookappe et al. 2015 (225)*	*Marcellis et al. 2015 (226)*	*Strookappe et al. 2015 (227)*	*Karadalli et al. 2016 (228)*	*Lingner et al. 2018 (222)*	*Naz et al. 2018 (181)*
COMPARATOR: Pre- and Post-fatigue scores (mean ± S.D. unless stated)	N/A	N/A	Pre: 30.3 ± 9.0 Post: 28.6 ± 9.0	Pre: 40.9 ± 15.8 Post: 31.1 ± 15.9 Mean difference: -9.6 (-15.4 to -3.8)	N/A	Pre (median): 45 (range 18-50) Median change in FSS: +1 points (range 0 to +4)
Statistical difference vs. comparator	Non-significant compared with baseline	P = 0.003 compared with baseline	Within group (intervention): p=0.009 Within group (placebo): p=0.408 Groups not directly compared	P = 0.71	P<0.0001 compared with baseline	P = 0.001 compared with baseline
Number of participants with clinically significant improvement	66% of patients with FAS >21 at baseline had improvement in FAS, not specified if MCID used	6 (3%) improve FAS by 4 points (MCID); 9 (50%) improved FAS by 10%	74.4% of intervention group and 48.5% of comparator group reduced FAS by 4 points (MCID).	Not stated	Absolute reduction fatigue (%): 11.5% Absolute reduction in severe fatigue(%): 18%	Not stated
Drop outs/ Side Effects	No withdrawals	6 patients withdrew; 3 = problems other than sarcoid 2 = health insurance problems 1= No reason	Not stated	No adverse events occurred	Not reported	No withdrawals
Evidence of treatment effect in fatigue	Unclear	Yes	Yes	No – both arms improved markedly over course of trial	Yes	Yes

FAS = Fatigue Assessment Scale; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy – Fatigue; MCID = Minimal Clinically Important Difference; FSS = Fatigue Severity Scale

Table 9 *- Risks of bias within trials reporting fatigue as an outcome measure (Pharmacological interventions)*

Author and Year	*Lower et al. 2007 (173)*	*Erckens et al. 2011 (105)*	*Heij et al. 2012 (207)*	*Van Rijswijk et al. 2013 (185)*	*Lower et al. 2013 (174)*	*Aggarwal et al. 2016 (223)*	*Baughman et al. 2017 (224)*
Sequence Generation	**LOW RISK** Random sequence computer-generated	**HIGH RISK** No randomisation (NOT RCT)	**LOW RISK** Computer generated randomisation code	**HIGH RISK** No randomisation (NOT RCT)	**UNCLEAR** No statement on randomisation procedure	**HIGH RISK** No randomisation (NOT RCT)	**UNCLEAR RISK** Participants randomised on 1:1 ratio but method of randomisation not stated
Allocation Concealment	**LOW RISK** Pharmacy-controlled allocation	**HIGH RISK** No concealment, all patients receive drug	**LOW RISK** Pharmacy-controlled allocation	**HIGH RISK** No concealment, all patients received drug	**UNCLEAR** No statement on allocation procedure	**HIGH RISK** No concealment, all patients receive drug	**UNCLEAR** No statement on allocation procedure
Blinding of participants, personnel and outcome assessors	**LOW RISK** Double-blind with low risk of breaking blinding	**HIGH RISK** No blinding	**LOW RISK** Only allocating pharmacist unblinded	**HIGH RISK** No blinding	**LOW RISK** Double-blind with low risk of breaking blinding	**HIGH RISK** No blinding	**LOW RISK** Investigators blinded though participants not blinded
Incomplete outcome data	**UNCLEAR** No description of missing data points or handling of missing data	**UNCLEAR** No description of missing data points or handling of missing data	**LOW RISK** Missing data compensated for by taking forward last value	**UNCLEAR** No description of missing data points or handling of missing data	**UNCLEAR** No description of missing data points or handling of missing data	**UNCLEAR** No description of missing data points or handling of missing data	**UNCLEAR** No description of missing data points or handling of missing data

Author and Year	***Lower et al. 2007 (173)***	***Erckens et al. 2011 (105)***	***Heij et al. 2012 (207)***	***Van Rijswijk et al. 2013 (185)***	***Lower et al. 2013 (174)***	***Aggarwal et al. 2016 (223)***	***Baughman et al. 2017 (224)***
Selective outcome reporting	**LOW** All outcomes reported	**UNCLEAR** No protocol available	**UNCLEAR** No protocol available	**UNCLEAR** No protocol available	**LOW** All outcomes reported	**UNCLEAR** No protocol available	**UNCLEAR** No protocol available
Other sources of bias	No other clear causes of bias identified; cross-over ensures groups balanced, patients are own controls. Small sample.	Study design (case series) limits conclusions – no comparator group to eliminate placebo effect.	Baseline imbalance in FAS and health status score (SF36) between groups – significantly lower fatigue scores in placebo arm. Small sample.	Retrospective review – data collected pre- and post-intervention but high risk of bias from retrospective nature	No other clear causes of bias identified; cross-over ensures groups balanced, patients are own controls. Small sample.	Study design (case series) limits conclusions – no comparator group to eliminate placebo effect.	RCT but no placebo arm so unable to exclude placebo effect on patient-reported outcomes including fatigue. Small sample size.
Overall risk of bias	**LOW** – Well designed cross-over trial, though only small sample	**HIGH** – Study design (case series) means no blinding, randomisation or comparator.	**LOW** – Well designed RCT *but* not powered to look at change in fatigue.	**HIGH** – Design (retrospective case series) has no blinding, randomisation or comparator.	**UNCLEAR** – Issues with description of randomisation allocation and concealment mean study at risk of bias	**HIGH** – Study design (case series) means no blinding, randomisation or comparator.	**UNCLEAR** – Issues with lack of placebo arm and description of randomisation, allocation and concealment mean study at risk of bias.

Table 10 *- Risks of bias within trials reporting fatigue as an outcome measure (Physical exercise interventions)*

Author and Year	*Strookappe et al. 2015 (225)*	*Marcellis et al. 2015 (226)*	*Strookappe et al. 2015 (227)*	*Karadalli et al. 2016 (228)*	*Lingner et al. 2018 (222)*	*Naz et al. 2018 (181)*
Sequence Generation	**HIGH RISK** No randomisation (NOT RCT)	**HIGH RISK** No randomisation (NOT RCT)	**HIGH RISK** No randomisation (NOT RCT)	**LOW RISK** Computer generated randomisation code	**HIGH RISK** No randomisation (NOT RCT)	**UNCLEAR** Sequence generation not stated; groups in sealed envelopes prepared by independent member
Allocation Concealment	**HIGH RISK** No concealment, all patients on programme	**HIGH RISK** No concealment, all patients on programme	**HIGH RISK** No concealment, all patients on programme	**LOW RISK** Evaluation and treatment were performed by different therapists	**HIGH RISK** No concealment, all patients on programme	**UNCLEAR** No statement on whether intervention and evaluation performed by different therapists
Blinding of participants, personnel and outcome assessors	**HIGH RISK** No blinding	**HIGH RISK** No blinding	**HIGH RISK** No blinding, including of assessors of physical function.	**LOW RISK** Subjects and investigators collecting data were blinded	**HIGH RISK** No blinding	**UNCLEAR** No statement on blinding of assessors to allocation
Incomplete outcome data	**UNCLEAR** No description of missing data points or handling of missing data	**UNCLEAR** No description of missing data points or handling of missing data	**UNCLEAR** No description of missing data points or handling of missing data	**UNCLEAR** No description of missing data points or handling of missing data	**LOW** Handling of missing data described	**UNCLEAR** No description of missing data points or handling of missing data

Author and Year	*Strookappe et al. 2015 (225)*	*Marcellis et al. 2015 (226)*	*Strookappe et al. 2015 (227)*	*Karadalli et al. 2016 (228)*	*Lingner et al. 2018 (222)*	*Naz et al. 2018 (181)*
Selective outcome reporting	**UNCLEAR** No protocol available	**UNCLEAR** No protocol available	**UNCLEAR** No protocol available	**UNCLEAR** No protocol available	**LOW RISK** Study protocol published before results published	**UNCLEAR** No protocol available
Other sources of bias	Not an RCT. Participants enrolling on programme would self-select as motivated people, generalisability limited	Not an RCT, also participants enrolling on programme would self-select as motivated people, generalisability limited	Patients choosing the intervention would be a self-selecting cohort; controls not randomised but refused intervention	Small sample. No other causes of bias identified.	Not an RCT, no comparator group; also participants enrolling on programme would self-select as motivated people, generalisability limited	Comparator group is usual care so not a true control group as no 'sham intervention'; will not control for non-exercise components of course (interaction with healthcare team, social aspects)
Overall risk of bias	**HIGH** - Study design (case series) means no blinding, randomisation or comparator.	**HIGH** - Study design (case series) means no blinding, randomisation or comparator.	**HIGH** – Self-selecting intervention group, high risk of bias given control group declined intervention	**LOW** – Well designed RCT, though only small sample	**HIGH** - Study design means no blinding, randomisation or comparator.	**UNCLEAR** – Issues with lack of true control group; limited description of randomisation, allocation and blinding mean study at risk of bias.

Systemic therapy: anti-TNF-alpha treatment and anti-inflammatories

Five trials evaluated interventions which have systemic or disease-modifying effects. Two investigated anti-TNF-alpha drugs (adalimumab and infliximab) (105, 185), one investigated ARA 290 (207), one investigated prednisolone and one investigated RCI (224). Only one trial, investigating ARA 290 (207), was a double-blinded, randomised, placebo-controlled trial; neither of the studies investigating anti-TNF-alpha therapies were of a randomised design, nor was the study investigating prednisolone. The study investigating RCI was single-blinded and had no placebo arm; the two arms of the trial were comparing two different doses of the drug.

Erckens and colleagues followed 26 sarcoidosis patients with refractory uveitis who had been commenced on Adalimumab (40mg subcutaneously once weekly) over a 12 months treatment period (105). All patients had previously received prednisolone and methotrexate. Fatigue was measured using the FAS, with 21 patients (80.7%) having a baseline FAS score >21 points. After the 12-month treatment period, there was a mean reduction in FAS score of 2.2 points and an improvement in FAS score in 14 of the 21 patients with a baseline FAS score >21 points; although it is not stated what constituted an improvement in the FAS and whether these patients met the MCID for the FAS score. The risk of bias is high with this trial design, as there is no comparator group to determine if this is a placebo-effect or natural progression of the disease, however, there is a suggestion that fatigue is improved by anti-TNF-alpha therapy.

In another study from the Netherlands, Van Rijswijk and colleagues (185) retrospectively reviewed 48 sarcoidosis cases who required treatment with Infliximab (5mg/kg intravenously at 0, 2, 6, 10, 14 and 18 weeks). All patients had previously received immunosuppression; 30 had received prednisolone and methotrexate, 12 received prednisolone only and 1 received methotrexate only. Data involving quality of life measures, including fatigue scores (within the CIS questionnaire), had been collected pre-treatment in the most recent 27 cases. The fatigue score improved by a mean of 5.3 points from a baseline of 49.4 points ($p=0.003$), although it is not clear if this is a clinically important improvement.

Furthermore, as this was a retrospective review, and without a comparator or placebo group, it is not possible to definitively attribute the change in fatigue scores to the intervention and does not conclude the benefits of TNF-inhibition in treating fatigue.

One study performed in Chandigarh, India, followed 51 consecutive cases of stage I or II pulmonary sarcoidosis treated with oral prednisolone commenced on 0.75mg/kg and reduced to zero over six months (223). Fatigue scores, measured by the FAS questionnaire, were measured before treatment and after treatment at six months; it was not clear if this was a pre-planned primary outcome. Of the 51 patients, 33 had pre-treatment fatigue (64.7%), with seven of these reporting severe fatigue (FAS score >34). Post-treatment, 21 patients showed an improvement in FAS scores of 4 points or more; four patients showed a clinically important worsening of their FAS score. All patients who initially complained of severe fatigue met the MCID for improvement in FAS score. Five patients who initially scored <22 on the FAS showed an increase in FAS score of >4 points. In total, nine patients showed a clinically significant deterioration in FAS scores (17.6%). Median change overall across all cases was 3 points (pre-treatment 24, post-treatment 21, p=0.004). This study is the only one to review the changes in fatigue after receiving corticosteroids, although these were newly-diagnosed cases and as such does not provide information on the effect of corticosteroids on sarcoidosis-associated fatigue in chronic cases. Post-treatment measures also occurred after receiving therapy, so it is unclear how fatigue scores changed whilst receiving prednisolone. Additionally, this was an observational study and it is unclear whether the changes in fatigue are treatment-related or the natural disease course after initial presentation with sarcoidosis.

A small multi-centre study by Baughman and colleagues investigated the use of RCI, a melanocortin peptide that is thought to be at least as effective as oral corticosteroids with reduced toxicity, for patients with advanced pulmonary sarcoidosis receiving prednisolone (224). This study enrolled only 18 patients, with 16 patients completing the 24 weeks of therapy in the study (eight patients in the 40 units twice weekly arm and eight patients in the 80 units twice weekly arm).

Participants were excluded if they had received anti-TNF therapy in the past 6 months or were being treated for pulmonary hypertension. The primary outcome was the reduction in dose of prednisolone, with fatigue (measured by the FAS score) recorded at baseline, week 7 and end-of-trial (week 24) time points. No results for change in fatigue are given by group; only changes across the entire cohort (both 40 units and 80 units twice weekly doses) are given for FAS scores. The cohort had baseline mean FAS scores of 28 points (range 15-46 points) and a reduction to a mean FAS score of 22 points (range 11-42 points) at week 24, a statistically significant reduction (p=0.0067). Eight patients had a reduction in FAS of four points or more at the end of the study compared with baseline. It is unclear if this was a dose-dependent effect as this was not discussed in the results. These results may reflect a reduction in prednisolone, which is known to cause fatigue through treatment side-effects (152, 165), or improved control of disease activity with the new treatment. However, the study was not powered to show improvement in fatigue, and the range of fatigue scores at 24 weeks shows that some participants remained significantly fatigued, with FAS scores as high as 42 points at the end of the study. Further work is required to compare the use of RCI with placebo and to ensure that improvements in FAS seen were not a placebo effect within this study.

Heij and colleagues (207) undertook a small double-blind, randomised controlled trial investigating the safety and efficacy of ARA 290 for symptoms of small fibre neuropathy in sarcoidosis patients. Only 12 patients were included in the active treatment arm. Of these patients, four were receiving steroids and 1 received a systemic anti-inflammatory drug. Participants were excluded if they received an anti-TNF drug within six months of the trial. Fatigue was measured using the FAS score, though this was a secondary outcome. The baseline groups were imbalanced with regards to fatigue (mean FAS 37.9 in the ARA 290 group, 33.6 in the placebo group), but despite the higher levels of fatigue in the treatment arm at baseline there was an identical reduction in FAS scores over the four-week trial period in both arms. There was no evidence that ARA 290 improved fatigue scores, but the trial was not powered for this outcome and was very short. It did show

improvement in its primary outcome (the small fibre neuropathy screening list) as well as being well tolerated; if a larger and longer trial investigating the drug were to be performed, measuring change in fatigue would be important to ensure that a treatment effect was not missed in this trial.

Neurostimulants

Two randomised-controlled trials, both using a cross-over design, investigated the use of neurostimulants for treating fatigue in sarcoidosis. One trial investigated the use of armodafinil (174) and one trial investigated dexmethylphenidate (173). In each trial the change in fatigue was the primary outcome being measured.

Lower and colleagues (173) treated ten patients with sarcoidosis-related fatigue with dexmethylphenidate and assessed its response by measuring fatigue using the FAS score. Participants received up to 10mg twice daily of dexmethylphenidate or matched placebo and were investigated weekly for eight weeks per arm (treatment and placebo). All patients were receiving at least one systemic agent for their sarcoidosis. Treatment effect in the intervention arm was seen after five weeks of therapy, with a mean reduction of five points in the FAS score after eight weeks of treatment. The number of patients meeting the MCID was not reported. The drug was well tolerated, with no withdrawals. The small scale of the trial means that the results should be interpreted with caution, but suggests clinical benefit.

In a cross-over trial by Lower and colleagues (174), fifteen patients with stable sarcoidosis received up to 250mg of armodafinil daily, all of whom underwent polysomnography and multiple sleep latency testing pre- and post-intervention. All participants had received systemic treatment for sarcoidosis (prednisolone, methotrexate, leflunomide, hydroxychloroquine, azathioprine or anti-TNF therapy) and nine were receiving continuous positive airway pressure therapy. There was a mean reduction of 4.5 points in the FAS score (the primary outcome) and nine patients (64%) exhibited a reduction of four points or more. Participants receiving armodafinil did have a prolonged sleep onset latency compared with placebo which was statistically significant, although it is not clear if this was a clinically significant

difference as no participants discontinued the medication due to insomnia. The paper did not report randomisation or allocation procedures, although it was double-blind and appeared an appropriate design for the study's aims. The small number of patients and short period of the trial suggest that further evidence is needed to confirm the efficacy of armodafinil in this setting.

Non-pharmacological treatment strategies

Six recent papers have investigated the effect of structured physical training programmes on fatigue in sarcoidosis and one study has looked at the effect of inspiratory muscle training on fatigue. Marcellis and colleagues (226) undertook an observational case-series study of twenty-four sarcoidosis patients in the Netherlands suffering with fatigue and/or impaired exercise tolerance. The intervention consisted of both upper- and lower-extremity peripheral muscle resistance training, with progressively increasing resistance through the training period, and endurance training, consisting of either treadmill or walking or cycling on an ergometer. Eighteen patients completed the entire training regime, with six not completing the programme. A statistically significant improvement was observed in FAS scores at the completion of the intervention: mean baseline and post-exercise FAS scores of 29.7 and 27.0 points respectively. Of the eighteen participants who completed the exercise programme, six patients (33.3%) had a reduction of four points in their FAS score; when using the alternative MCID of a 10% reduction, nine patients (50%) met this criterion. This study had no comparator group, it did not state how many patients were approached or screened for inclusion, and patients entering the trial and completing the exercise programme are likely to have been motivated to undertake such an intervention. Although the results from this study suggest that the intervention is beneficial for sarcoidosis-associated fatigue, it is unlikely to be beneficial in all patients.

Strookappe and colleagues (227) investigated physical activity programmes in a similar cohort of Dutch sarcoidosis sufferers in a retrospective observational study. From an initial cohort of 147 sarcoidosis patients who had undergone physical

performance assessment, 49 patients undertook a 12-week supervised exercise programme. This was similar to that described by Marcellis and colleagues, with the peripheral muscles strengthening individualized for each patient. Twenty-one (42.9%) of the group were receiving steroids. A comparison was made with 41 sarcoidosis patients who had chosen not to undertake the programme but undertook identical physical assessments. Following re-assessment at the end of the 12-week period there was a statistically significant within-group improvement in FAS scores in those who received physical therapy (29.8 pre, 25.6 post, p=0.009) whereas the comparator group had a non-significant reduction (pre 30.3, post 28.6, p=0.408). In the exercise programme group, 74.4% of patients had an improvement in their FAS score of four points or more, although 48.5% of the comparator group showed the same reduction despite not receiving any intervention. The within-group results suggest that physical training may be beneficial for fatigue, though the results should be interpreted with caution. As with the other trials investigating exercise programmes on fatigue, participants within the trial would have self-selected as a group keen to undertake the intervention. Even given this source of bias, patients who chose not to receive the intervention reported a clinically significant improvement in their fatigue. Finally, although the authors state that blinding was not possible in this trial, it would be possible to blind assessors to patient groups when assessing physical and psychological parameters pre- and post-intervention; whether this occurred was not stated in the paper.

Strookappe and colleagues (225) also investigated the physical training in patients with end-stage sarcoidosis-related pulmonary fibrosis, alongside a cohort with idiopathic pulmonary fibrosis (IPF). Twelve patients with stage IV sarcoidosis participated in a 12-week exercise programme, similar to those described in the previous trials (226, 227). Patients were recruited from the same centre and during the same period as those included in another study by the same authors (227), though it is not specified whether these patients were also included in the results from the earlier study. Despite this, the study was included as it reported the results of a sub-group of patients with end-stage pulmonary sarcoidosis, which were not reported separately in the other paper. FAS score was measured pre- and

post-intervention. Baseline mean FAS score was 25.1 in the sarcoidosis group, with only six patients (50%) having clinically significant fatigue. Following the programme, four of the six patients reported improved fatigue, although the paper does not state whether participants that improved met the MCID for the FAS score. This study did not have a non-intervention group, and only a small number of participants with fatigue at baseline were included. The same source of biases existed as described with the other two studies investigating this intervention, making it difficult to be confident of the effect of physical training programs for sarcoidosis patients suffering fatigue.

Another study including advanced sarcoidosis was performed in Turkey. Naz and colleagues included 18 patients with stage III or IV sarcoidosis, randomised to either a supervised 12-week exercise programme with twice-weekly session or usual care only (181). Participants were recruited from a hospital ILD clinic and the course was individually tailored based on the disease severity and level of symptoms. The primary outcome was change in 6-minute walk distance but fatigue was measured as a secondary end-point using the FSS. Average FSS scores were over 36 points indicating significant fatigue at baseline, with a significant change seen between the intervention and usual care groups at the end of the programme (median change -7 points vs +1 points, p=0.001); this occurred despite baseline FSS score being five points higher (median score) in the intervention group compared with the usual care group. The study is limited by the small number of participants and the lack of sham intervention to control for increased contact with the health professionals and/or other patients in the intervention group, it also fails to mention blinding of outcome assessors to intervention group. The results are in line with previous evidence indicating benefit in multiple aspects of quality of life, including fatigue, in patients undergoing a structured and tailored exercise programme.

The largest study to date investigating the potential benefits of a structured exercise/rehabilitation programme was performed by Lingner and colleagues (222). The study included 296 cases undergoing a 3-week intense rehabilitation programme, including endurance training, strength training, patient education and group sessions with a respiratory physiotherapist; additionally, optional

components could be undertaken including inspiratory muscle training, relaxation training, and counselling. Early outcome data collected immediately following completion of the rehabilitation programme showed a mean reduction in FAS score of -4.09, from a baseline mean score of 26.6 points. Additionally, the study recorded the number of patients reporting fatigue as a "main clinical symptom" pre- and post-treatment; 78.5% of patients reported fatigue as such, with 33.5% describing it as very severe. At the end of the study, 72.4% of patients still reported fatigue as a symptom and 22.3% rated it as very severe; no analysis was performed to explore whether this was a statistically significant drop, although a 10% absolute reduction in patients reporting fatigue as a present symptom appears to be a marginal clinical benefit. The results are in keeping with earlier papers suggesting benefit on fatigue scores from pulmonary rehabilitation but in a much larger number of patients. The lack of a comparator group limits the conclusions that can be drawn on the benefit on fatigue scores compared with not undertaking a structured rehabilitation programme. Mean change in FAS score suggests marked benefit but the number of patients still reporting fatigue as a symptom at the end of the programme suggests that it may only have a large benefit on fatigue for a modest number of patients.

Finally, a study undertaken in Turkey measured change in fatigue as a secondary outcome in patients undergoing an inspiratory muscle training programme. Karadalli and colleagues performed a randomised-controlled trial in patients with stage I or II sarcoidosis, with a 6-week programme of moderate intensity inspiratory muscle training, with the primary objective of improving dyspnoea scores (228). Fatigue was measured using the FSS, a nine-item questionnaire with a maximum score of 63 points; no threshold for significant fatigue has been determined although the MCID is estimated at 20.2 points (229). Additionally, this score has not been validated in cohorts with sarcoidosis. Both the treatment and control group had similar FSS scores at baseline (39.2 +/- 14.9 vs 40.9 +/- 15.8). Both groups saw statistically significant improvements in FSS score (-8.0 (-14.4 to -2.0), p=0.01 in the treatment group; -9.6 (-15.4 to -3.8), p=0.002 in the control group), although neither reached the MCID for the FSS tool and no difference in treatment effect

was seen between the groups (p=0.71). The study was small, with only 15 patients in each arm, and no justification for the sample size was given so it is unclear whether it was powered for its outcomes. These results suggest that inspiratory muscle training, as opposed to a more general physical training programme, does not improve fatigue levels compared with a sham intervention.

Excluded Studies of Interest

Although the search strategy identified thirteen relevant studies, an additional four papers were identified that did not meet the inclusion criteria but provided relevant data regarding potential therapies for sarcoidosis-associated fatigue. Two studies investigating anti-TNF-alpha therapy in large cohorts were not included in the systematic review; the first had no measurement of pre-treatment fatigue scores and the second failed to describe a quantitative change in fatigue (125). One article describing methylphenidate use for sarcoidosis-associated fatigue was excluded because it was not a full article and did not describe a baseline fatigue score. Furthermore, one cross-sectional study has suggested that the anti-malarial hydroxychloroquine may have benefits on fatigue.

One study investigating cognitive failure and sarcoidosis-associated fatigue in 343 patients was excluded as baseline assessment of fatigue occurred after patients had already been established on treatment (208). The study was a six-month cross-sectional assessment of patients who had already received various therapies, including TNF-inhibition in 42 patients. The results showed an improvement in FAS scores in the anti-TNF alpha therapy group over six months (baseline FAS 32.8+/-7.31, six-month change -4.90+/-5.57) when compared with patients on no treatment (baseline FAS 28.6+/-7.94, six-month change 0.44+/-5.13), or on corticosteroids with or without antimetabolite (methotrexate) therapy (baseline FAS 28.2+/-7.81, six-month change +1.19+/-4.87). The patients in the anti-TNF-alpha therapy group had higher fatigue scores on their initial questionnaires compared with the other groups, and after six months there was no difference in fatigue scores between patients receiving other forms of therapy. However,

without baseline characteristics in each group before commencing treatment it is not possible to directly compare the results of the groups or establish the effect of treatment on fatigue scores.

A further study investigating TNF-inhibitor treatment in sarcoidosis patients (adalimumab or infliximab) recorded pre-treatment fatigue levels in 111 patients was excluded because no numerical data for change in fatigue measure (FAS) were included (125). All patients had received prednisolone and methotrexate before receiving TNF blockade and had evidence of ongoing disease activity despite treatment. Of the 111 patients included, 100 (90.1%) reported a FAS score >21 (mean baseline FAS 33.0) and 59 reported severe fatigue (FAS score >34). After 12 months of therapy 60 patients who were fatigued at baseline had improvement in their fatigue score; unfortunately, the definition of improvement and the scale of change in the FAS score required to be classified as a responder are not stated, therefore it is not possible to evaluate whether the intervention was clinically effective from these results.

Methylphenidate was used in a series of five patients with severe sarcoidosis-associated fatigue that was described in a letter from Wagner and colleagues (230). Five patients received 10mg twice daily of methylphenidate. There was no formal measure of baseline fatigue severity but the paper describes a statistically significant reduction on the “Symptoms of Fatigue” scale after one month. There were positive reports from four of the five patients, with two reporting that they felt their lives were “back to normal”. The five patients continued methylphenidate long-term; at two-years, all five of the patients remained on methylphenidate and reported continuing improvement in fatigue, although no formal fatigue scoring was performed. The authors concluded that further studies in larger groups of patients are required, though at the time of writing only the two small cross-over studies of armodafinil and dexmethylphenidate have been undertaken.

Although no papers directly investigated the use of chloroquine or hydroxychloroquine for fatigue, a possible effect of the drug on fatigue scores was noted in a cross-sectional study comparing two cohorts of sarcoidosis patients (113). This paper was not included in this systematic review as it did not report

change in fatigue scores pre- and post-treatment, but the authors noted that patients receiving hydroxychloroquine (n=22) had lower fatigue scores than patients on other agents in the absence of any other differences in disease activity or severity. The lack of pre- and post-treatment fatigue scores, as well as the small number of patients receiving the agent, mean that conclusions about the effectiveness of hydroxychloroquine for treating fatigue cannot be directly drawn from these results.

2.4 Discussion

The evidence base for treating fatigue in sarcoidosis is limited. Although 13 trials were identified, all of which are presented here, all the studies were either small or were of poor-quality study design, leading to the possibility of inherent biases affecting the results. This makes it difficult to draw strong conclusions about the benefits of each therapy.

In patients with clinically significant fatigue with evidence of disease activity despite appropriate use of first- and second-line immunosuppressants, anti-TNF-alpha therapy may be indicated. In the absence of active, organ-threatening disease the risks and potential side-effects of these drugs make them difficult to recommend for treating fatigue alone. The findings from the use of RCI suggest that patients on significant doses of corticosteroids may benefit from additional therapy to help reduce their corticosteroid dose; given the small number of participants in the RCI trial it is not yet possible to recommend this therapy, but the use of other steroid sparing therapies such as methotrexate may be indicated where fatigue is felt to be a side-effect of steroid therapy itself. Prednisolone use itself, for a six-month period, appeared beneficial for new diagnoses where fatigue was present alongside respiratory disease requiring treatment, though it is impossible to say if this was the natural history of fatigue in new cases of sarcoidosis due to a lack of control arm in the one study investigating steroids.

Hydroxychloroquine is considered effective for treating cutaneous sarcoidosis (231), but its use in patients with sarcoidosis-associated fatigue who require

corticosteroid therapy has been suggested in a previous review (232). The possible effectiveness of treating fatigue with this agent is interesting, but evidence from trials investigating pre- and post-intervention fatigue scores is needed before stronger recommendation can be made for its use. The current evidence base for using these agents for sarcoidosis-associated fatigue is insufficient to draw any conclusion about its effect on sarcoidosis-associated fatigue.

The management of fatigue in patients with quiescent disease is often a clinical challenge, especially given the potential side effects of disease-modifying medications. Neurostimulants such as modafinil or methylphenidate may be appropriate in these cases. The two trials investigating these interventions were well designed, but only included a small number of patients. Long-term use of these medications has been safe in other conditions (ADHD) but the trials investigating their use in sarcoidosis have been very short. Furthermore, both studies investigating neurostimulants were cross-over trials, a design which has been suggested as an inappropriate design for trials investigating the use of methylphenidate, although these recommendations relate to its use in trials involving patients with adult ADHD (233). The primary reason for this is the inability to maintain blinding when using an agent with detectable positive effects and characteristic adverse effects, such as neurostimulants, which can eliminate any controlling for placebo effect. In adult ADHD, this has been seen in the results of previous trials. A meta-analysis showed that stimulants had a larger effect size in these patients when studied in cross-over trials compared with parallel-arm trials (234). This finding may be related to the removal of between-patient variability seen in parallel-arm studies, but could also be related to the susceptibility to expectancy effects from difficulty maintaining blinding, a factor highlighted by a Cochrane review previously (235). Future parallel-arm studies investigating the effect of neurostimulants on sarcoidosis-associated fatigue are required to better understand their effect.

Beyond pharmaceutical intervention, physical exercise programmes appear to lead to improvements in fatigue scores, but in the one trial that had a comparison group almost half of the controls demonstrated clinically significant improvements in

fatigue without any intervention. The largest study, ProKaSaRe, showed evidence of benefit through the use of FAS scores, although the absolute number of patients still reporting fatigue as a main or significant symptom only reduced by approximately 10 percentage points (absolute reduction), suggesting that a marked benefit may be felt by some but that a large number of patients still suffer with the symptom following completion of the programme. The patients who did enrol on the exercise programmes were likely to have been motivated to undertake this and therefore most likely to benefit. It should be noted that the evidence for improvement in patients with sarcoidosis-associated fatigue was only seen with structured general physical exercise programmes, not specific inspiratory muscle training. These findings are in line with current understanding on the positive impact of graded exercise in patients with CFS (236), although the evidence from CFS is from self-guided graded exercise with minimal input from physiotherapists, in contrast to the structured programmes utilised in studies here. For patients with physical limitation and fatigue who express an interest in undertaking physical therapy, a structured exercise programme may provide benefits. This may be undertaken alongside other pharmacological interventions, either for underlying disease activity or to directly treat the symptom of fatigue, as part of an agreed plan between physician and patient to manage sarcoidosis-associated fatigue. Consideration must be given to alternative strategies beyond rehabilitation programmes for patients where fatigue persists despite having undertaken such an intervention without benefit.

There were limitations to the methodology of this review. The review included only English language papers. No foreign language articles were identified from the search strategy, due to the non-MeSH search terms being English only. Although efforts were made to contact authors regarding missing data or unclear elements of trial design some gaps remain in the data presented here. The main limitation when drawing conclusions from the data relates to bias within the studies included.

Future research considerations

The main limitation of the evidence base for managing fatigue is the lack of trials of sufficient sample size or duration to make firm recommendations for managing patients with fatigue in clinical practice. Much of the data available are from observational studies or studies of less than 30 patients. Only one study included more than 100 patients but this was not a randomised or controlled study. Any future trials investigating therapies for treating sarcoidosis should include fatigue as an outcome measure given the frequency and significance of fatigue in sarcoidosis cohorts, consistent with suggestions by WASOG (166); this would allow a greater evidence base around the effect of treatment modalities on fatigue scores.

In patients with quiescent disease, where fatigue is the primary symptom driving treatment decisions, more randomised placebo controlled clinical trials are required. The need to eliminate any placebo effect is important; in one of the trials included in this review (207) almost identical changes in fatigue from baseline were seen in both intervention and placebo arms. Designing these trials appropriately to inform clinical decision making is therefore the primary concern. The randomised trials that have already been performed have been very short; either four- or eight-weeks duration. Clinical use of agents such as neurostimulants would likely be over many months and future trials should therefore assess change in fatigue scores and tolerability of medications over a much longer period of time than previously seen, and at least six months.

2.5 Conclusions

The neurostimulants methylphenidate and modafinil offer the potential to provide symptomatic relief to patients with sarcoidosis-associated fatigue. Given the limitation of existing evidence for neurostimulant agents, designing a study investigating the efficacy of these drugs is an important step in determining whether they should be used as part of the care for patients with sarcoidosis who experience significant fatigue. A number of considerations remain when considering how best to design a full study powered to investigate this; for this

reason, a feasibility study would be beneficial to determine how to best design a full phase III study.

An additional question relates to the benefits of exercise on sarcoidosis-associated fatigue and the direction of effect; if increasing exercise can improve fatigue, will improving fatigue lead to an increase in daily activity? To understand this, any future trial investigating the effect of a pharmaceutical intervention on fatigue scores would benefit from a review of exercise and activity levels. If medication-driven improvements in fatigue improve physical exercise levels, these improvements may further improve fatigue and may allow reduction or even discontinuation of medications after a sufficient time period. Measuring activity levels can be problematic; determining the preferred way of doing this would be beneficial for any future study.

In the next chapter, the findings of a pilot study of wrist-worn activity monitors in patients with sarcoidosis are presented. This forms the first step towards performing a feasibility study of the neurostimulant methylphenidate. The importance of measuring exercise levels in any study monitoring change in fatigue has been discussed above. In order to enable accurate measurement of activity it is important that a device is used with is acceptable to patients so as to maximise the likelihood of the device being worn and capturing the most data possible. In order to ensure an appropriate device is used, a comparison study of two widely used accelerometer devices is presented, the results of which will be used to identify the preferred device for use in the subsequent feasibility study, “Fatigue and Sarcoidosis – Treatment with Methylphenidate” (*FaST-MP*).

Chapter 3: *Determining a preferred measurement device for recording daily activity in patients with sarcoidosis – a pilot trial of two wrist-worn accelerometer devices*

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Clinical Trial – Registered with clinicaltrials.gov
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Research Ethics Committee (REC) Approval Gained
REC reference - 15/SW/0363

3.1 Introduction

In the previous chapter, the importance of exercise in fatigued patients was discussed, with multiple studies investigating structured exercise courses as an intervention to improve fatigue scores. The interaction between exercise and fatigue may be bi-directional, with improvement in fatigue levels potentially improving exercise levels. To determine this, the *FaST-MP* feasibility study was developed to include objective measures of daily activity, planning to use a wrist-worn activity monitor to track changes in participants' daily activity before, during and at the end of the study. Before this can be undertaken it is important to determine which device should be used within the trial. A short pilot study of two widely-used activity monitors was undertaken to determine a preferred device by participants in order to maximise the likelihood of obtaining valid activity data from participants in the *FaST-MP* study.

Background

The ability to quantify daily physical activity is important when evaluating interventions where levels of exercise during daily living can be used as an outcome measure. The presence of mental fatigue, such as that seen in patients with sarcoidosis (170), leads to declines in endurance performance and higher perceived exertion, suggesting that exercise performance is regulated by the central nervous system (237). The potential use of neurostimulants, such as methylphenidate, can improve exercise capability in healthy individuals (238). The use of methylphenidate for the treatment of sarcoidosis-associated fatigue therefore may improve physical activity levels; for this reason, the change in measured physical activity was a planned secondary outcome measure within the FaST-MP feasibility study. Measures of exercise capability in clinic-based tests (six-minute walk distance) have not been shown to change in patients who have received methylphenidate compared with placebo (239). Six-minute walk tests (6MWT) are likely to be sub-maximal for patients without significant cardiovascular limitation (240). Furthermore, measuring physical activity in free living allows a global overview of both exercise capability and volition, the latter of which may be markedly affected

by mental fatigue; therefore, measurement of physical activity in free-living conditions could be an important outcome variable to measure in order to understand the effect that methylphenidate has on patients with sarcoidosis-associated fatigue.

Measuring physical activity in free-living conditions is widely undertaken using questionnaires. These ask participants to recall the amount of exercise that they have undertaken during a defined period. The use of these activity questionnaires is associated with recall bias. Other methods, including the use of accelerometry-based activity monitors, offer the possibility of measuring activity objectively (241). Accelerometers have been shown to produce comparable results to double-labelled water, the gold-standard measurement of energy expenditure, and can provide information on activity patterns rather than total energy expenditure over a set period (199). Some accelerometers are also able to measure sedentary behaviours comparable to the gold-standard measure of inclinometers (242-244).

Activity monitors can either be worn proximally on the hip or upper arm, or distally on the wrist or ankle. The wrist position is associated with a reduction in accuracy when classifying activity intensity compared with the hip position, potentially due to constraint of movement at the wrist when performing certain activities (245). However, wrist-worn devices benefit from being more acceptable to participants and may therefore lead to better compliance and improved wear time (246). For this reason, wrist-worn devices are often preferred for measurement of physical activity in free-living conditions, as is the case in the UK Biobank and the USA NHANES projects. There are a number of wrist-worn devices available, yet it is unclear how much impact the individual design has on the comfort of wearing the device, as well as the subsequent effect on wear time.

It has been suggested that activity levels are reduced in patients with sarcoidosis, particularly when suffering from fatigue (145), and that improving physical activity can improve fatigue scores (226, 227). Although the link between sedentary behaviours (defined as sitting or lying with low energy-expenditure) and fatigue has not been investigated in patients with sarcoidosis, an inverse correlation between them has been seen in other conditions where fatigue is a prominent symptom,

such as fibromyalgia (247) and rheumatoid arthritis (248). Furthermore, it has previously been suggested that when considering choice of device for future studies within a patient group that a pilot study be performed to determine the ideal accelerometer device (249). As part of this thesis, within the *Fatigue and Sarcoidosis – Treatment with Methylphenidate* (FaST-MP) feasibility study presented in Chapter 4, measurements of physical activity in free-living conditions were planned. In preparation for this, a pilot study of two commonly-used devices was undertaken to determine which device is preferred by patients with sarcoidosis, aiming to improve the likelihood of collecting valid data from participants within FaST-MP.

Choice of accelerometers

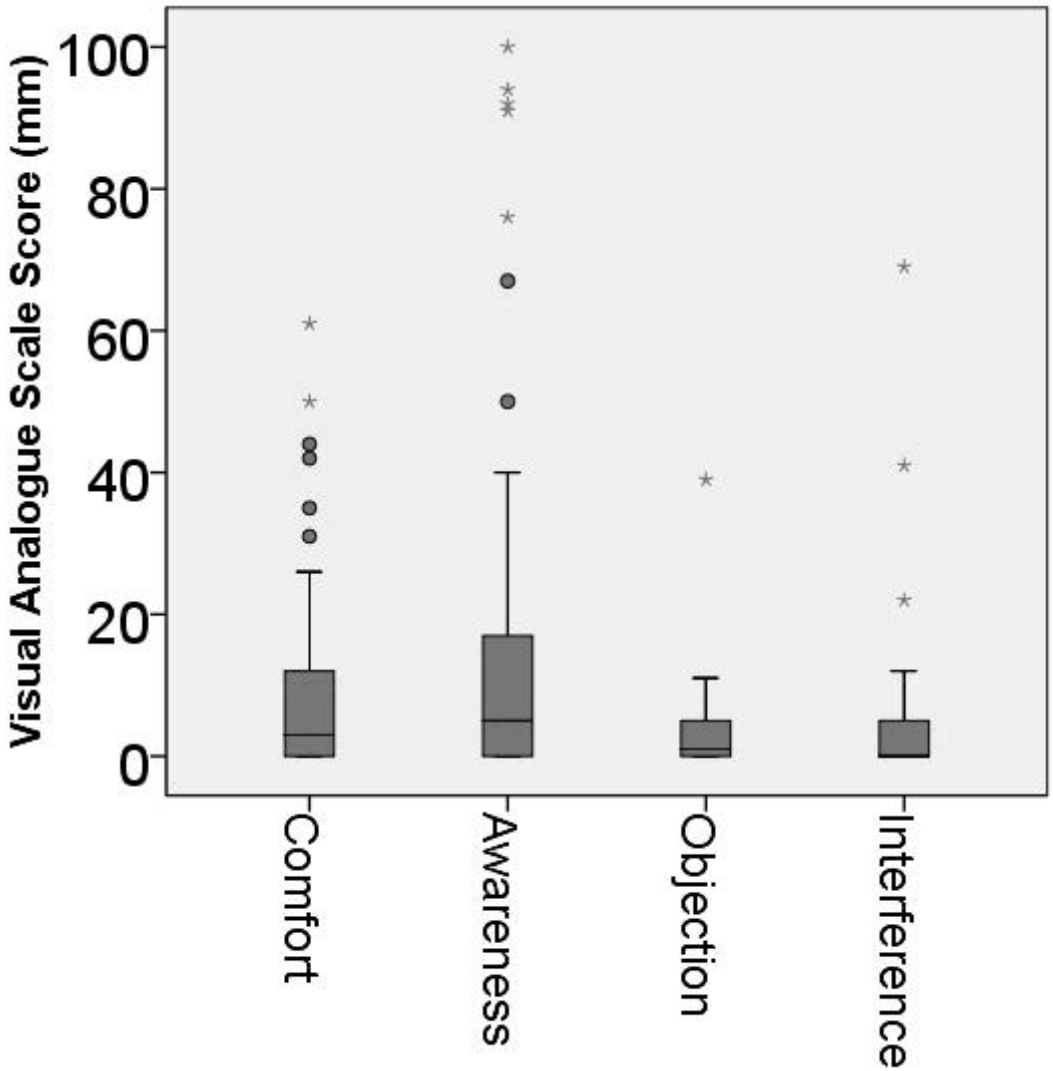
This study investigates the relative acceptability of two widely-used wrist-worn accelerometry-based activity monitors, the Actigraph GT3X-bt and the GENEActiv original, in patients with sarcoidosis. The GENEActiv device has been used previously in large studies investigating activity patterns, including the Whitehall II study (250) and Fenland cohort (202) in the UK, and the Pelotas cohort in Brazil (251).

We have previously undertaken our own work using the GENEActiv original device in patients with idiopathic pulmonary fibrosis (IPF), a form of progressive fibrosing interstitial lung disease (252). The device was chosen to evaluate the association between time spent in sedentary behaviours with measures of pulmonary function, exercise capacity and quality of life. Thirty-nine patients wore the GENEActiv original device for seven days. Data was collected from participants recording their perception of the device through a questionnaire. This recorded each participant's rating of the device's comfort, their awareness of the device whilst wearing it, their objection to wearing the device and how much the device interfered with daily life; each of these outcomes was rated on a 100mm visual analogue scale, with lower scores indicating a better rating. In addition, we assessed the number of

participants recording "valid" data, defined as at least 16 hours of data from two weekdays and two weekend days.

The results of the visual analogue scale questionnaire are shown in Figure 4; mean scores in each domain were low confirming that the devices were well perceived by participants. Thirty-five (89.7%) of the participants recorded valid data during their wear period, with two of the device failures occurring due to incorrect set-up prior to wearing. Only two participants did not wear the device for sufficient time to record valid data.

Figure 4 *- IPF patient perception of GENEActiv devices; visual analogue scale results*



On the basis of these positive results, the GENEActiv device was chosen as one of the two devices to trial prior to use in the planned feasibility study for investigating the use of methylphenidate in sarcoidosis-associated fatigue.

The Actigraph GT3X-bt was chosen as the comparator for the GENEActiv device. The GT3X-bt has been shown to be reliable in recording activity, and continues to be used widely as a method of measuring activity (253). These Actigraph and GENEActiv devices are different in design but both output raw data which can be analysed in an identical fashion (243, 254). Both have also been shown to be able to measure sedentary behaviours from postural data (242, 243), an important advantage over a number of competing devices.

Study objectives

The objective of this study is to determine which wrist-worn activity monitor is preferred by patients with sarcoidosis. The primary outcomes of interest are patient preferences relating to device comfort and wear time of the devices. The secondary outcomes of interest are patterns of activity and sedentary behaviours in these patients, and the correlation between these outputs and the fatigue questionnaire scores, although the study is not powered for these secondary outcomes.

3.2 Methods

Subjects

The study was undertaken at the Norfolk and Norwich University Hospital, in the UK. Patients with a diagnosis of sarcoidosis were eligible for inclusion. The requirement for a diagnosis of sarcoidosis was either (1) a previous biopsy confirming non-caseating granulomas consistent with sarcoidosis, or (2) previous discussion by multi-disciplinary interstitial lung disease meeting panel with consensus diagnosis of sarcoidosis. All participants had to be aged 18 years old or over and able to provide written consent. Ethical approval for the study was gained

from the South West – Central Bristol Research Ethics Committee, reference number 15/SW/0363. The trial was registered on clinicaltrials.gov, reference NCT02626897.

Seventeen patients were approached to take part in this study; twelve consented to participate. All participants wore both devices for seven days each in a cross-over manner. The order in which the devices were worn was allocated randomly based on a computer-generated code.

Clinical Assessments

Data regarding body mass index (BMI), forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC) and FEV1/FVC ratio were taken from the most recent clinic attendance. Data was recorded on current immunosuppression use, organs affected by sarcoidosis (stratified into pulmonary and extra-pulmonary disease), and duration since diagnosis. All participants completed the FAS questionnaire, a ten-question fatigue score with a maximum score of 50, as a measure of present levels of fatigue. Higher scores indicate greater levels of fatigue, with the threshold for significant fatigue in the FAS score being 22 points or greater (112).

Recording of device preference

All participants were asked to complete a survey documenting their impression of each device immediately after completing the period of wear for each. The questionnaire consisted of four 100 mm visual analogue scales (VAS), previously piloted in an earlier study using wrist-worn accelerometers to measure activity over a seven-day period (252), with participants asked to mark on the 100 mm scale their response to each of the following questions; (1) How comfortable was the device to wear? (2) How aware of it were you? (3) Would you have any objection to wearing it again? and (4) To what extent did it interfere with daily life? The VAS was scored by measuring the distance along a line from the left-hand side that the mark

was made; a score of zero (0 mm) referred to no problems for each question and a score of 100 (100 mm) indicated severe or constant problems for each question. In addition to these four questions, participants were asked to complete a free-text box detailing any difficulties that were encountered with either device.

Measurement of daily activity

The two wrist-worn devices chosen for comparison were the GENEActiv original device (Activinsights, Cambridgeshire, UK) and the Actigraph GT3X-bt device (Actigraph, Pensacola, Florida, USA). The GENEActiv is a tri-axial, accelerometer-based activity monitor with a dynamic range of +/-8g (where g is equal to the gravitational pull of the earth), measuring 43 x 40 x 13mm with a traditional plastic watch strap, and weighs 16 grams. The Actigraph GT3X-bt is also a tri-axial, accelerometry-based activity monitor with a dynamic range of +/-6g, measuring 46 x 33 x 15mm with a Velcro-fixing strap, and weighs 19 grams. It has been widely used for both hip-worn and wrist-worn monitoring of activity. Because the primary outcome was determining in the acceptability and comfort of the devices, devices were worn separately over consecutive periods rather than simultaneously.

Each device was worn for seven days by each participant on their non-dominant wrist. Devices were initialised to record data over the seven-day period and then returned via postal envelopes. They were set to record output from the accelerometer thirty times per second (i.e. sampling frequency 30Hz). Data was defined as 'valid' if the devices were worn for at least 10 hours per day for at least two weekdays and two weekend days; the number of patients meeting a higher threshold of 16 hours per day were also recorded in keeping with previous studies (255). Finally, the number of days with 24 hours of wear time within each recording period was noted.

Activity data was analysed for both time spent in thresholds of activity (light, moderate and vigorous), as well as sedentary time. The mean accelerometer outputs by magnitude of wrist acceleration (Euclidean norm minus one-g, ENMO) per 24 hour period, during the least active 5 hours (L5) and most active 5 hours (M5) were calculated using the *R*-statistics package GGIR (256). Time spent in

moderate or vigorous physical activity (MVPA) was calculated using the threshold of 100milli-g as has been used previously (251, 254) and is close to the specific device outputs signifying the threshold for moderate activity for both the GENEActiv (93.2milli-g) and Actigraph (100.6milli-g) devices, which have been established in previous data (257). MVPA was also calculated by 'bout' criteria as per WHO recommendations of activity occurring in bouts of at least ten minutes (258), using thresholds of more than 80% of any ten minute epoch spent above the 100milli-g threshold to be counted ($MVPA_{10}$). Magnitude of difference in outputs between devices was calculated where minimum valid data was available from both devices for a participant.

In addition to the output from GGIR, data from the preferred device (from the reported preference and total wear-time) was analysed for time spent in sedentary behaviours using the sedentary sphere custom spreadsheet (available elsewhere (242)) after raw data from the devices had been converted into .csv format in 15-second epochs. Thresholds for activity vigour within this spreadsheet were taken from previous data by Esliger et al (259) and adjusted for the sampling frequency of the accelerometers, leading to differences in calculated time spent performing moderate or vigorous activity compared with the GGIR output.

Statistical analysis

All data analysis was undertaken by SPSS Statistics version 22 (IBM Corp, Illinois, USA). Comparison of device outputs and participant experience by each brand of accelerometer was undertaken. Visual analogue scores of device acceptance between devices were compared using the paired t-test. Wear time was calculated in minutes per day, averaged over the entire seven-day period, and compared using the paired t-test. The number of full 24-hour periods recorded during the seven-day window were also compared using this method. The number of devices which recorded any data and the number of devices recording valid data at both the lower and higher thresholds, defined in the previous section, were compared using the chi-squared test. Differences in activity measurements (ENMO, L5, M5, MVPA and

$MVPA_{10}$) between the two accelerometer outputs were compared using the magnitude of difference between paired samples. Where a participant returned both devices with minimum valid data on both devices, no statistical test was applied due to the small number of samples. Spearman's correlations between FAS scores and time spent in sedentary behaviours and each threshold of activity was calculated using data from the preferred device.

3.3 Results

Baseline demographic data for the participants are shown in Table 11. All 12 participants had pulmonary sarcoidosis and five participants (41.7%) had extra-pulmonary disease. Five participants were receiving immunosuppression at the time of inclusion. Nine participants (75%) scored more than 21 on the FAS score, indicating significant fatigue.

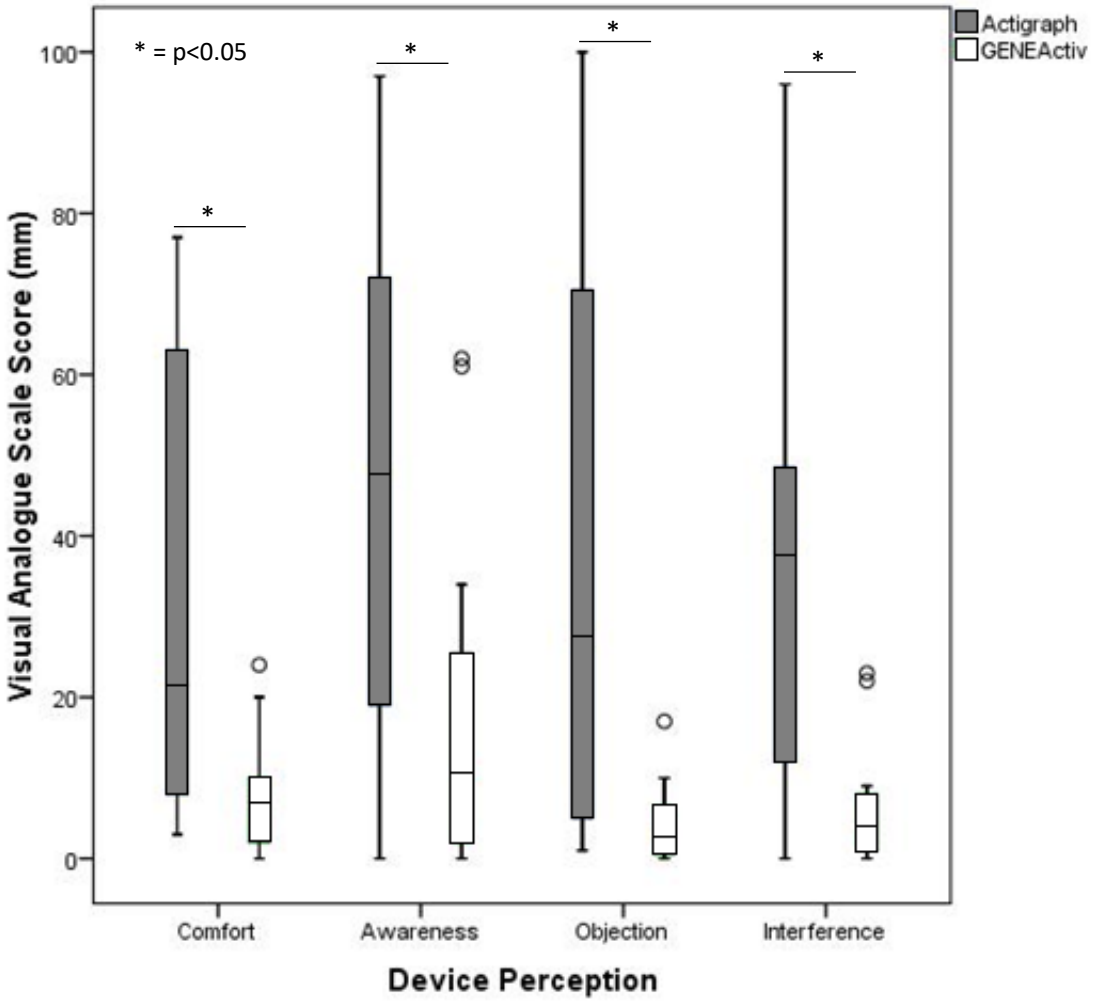
Table 11 *- Participant characteristics at baseline*

Baseline Characteristic	**Value** ***Mean (S.D.) unless otherwise specified***
Age – years (S.D.)	54.5 (13.0)
Male gender (%)	7 (58.3)
BMI – kg/m^2 (%)	27.3 (4.7)
Years since diagnosis (S.D.)	8.9 (8.7)
Pulmonary disease (%)	12 (100)
Extra-pulmonary disease (%)	5 (41.7)
- **Cardiac**	- 2
- **Cutaneous**	- 2
- **Ophthalmological**	- 1
On immunosuppression (%)	5 (41.7)
- **Prednisolone**	- 4
- **Methotrexate**	- 1
- **Azathioprine**	- 1
- **Methylphenidate**	- 1
FEV1 – % predicted (S.D.)	78.9 (23.2)
FVC – % predicted (S.D.)	74.8 (40.5)
Ratio (S.D.)	75.1 (16.6)
Fatigue Assessment Scale (FAS) Score (S.D.)	28.8 (9.3)
- ***FAS >21 (%)***	- *9 (75)*

The GENEActiv device was preferred by ten (83.3%) of the participants in this study. The results from the VAS questionnaire regarding experience of the devices are shown in Figure 5. Statistically significant differences ($p<0.05$) were seen between the devices, with the GENEActiv device being more highly rated by participants across all domains of comfort, awareness of the device, objection to wearing the device and interference with daily activities. Comments against the Actigraph device included being 'too bulky '(three participants) and the 'Velcro strap was too uncomfortable' (three participants). Despite this, all but one of these participants recorded at least minimum valid data. Two participants preferred the Actigraph to the GENEActiv device; one person found the GENEActiv strap uncomfortable and another developed a skin reaction to the strap, although both of these participants

recorded sufficient data to be considered valid monitoring periods. Other comments against the GENEActiv referred to the lack of a watch-face on the device.

Figure 5 *- Box-whisker plots of Visual Analogue Scale scores for experience of Actigraph and GENEActiv devices*



Amongst the twelve patients who wore an accelerometer, 11 (91.7%) of the GENEActiv devices and 9 (75%) of the Actigraph devices recorded the minimum 'valid' data (Table 12). Results for the number of devices returned with any data, the number of devices returned with valid data and the mean duration of daily

wear time is shown in Table 12. Preference for the GENEActiv device was reflected in greater wear time compared with the Actigraph device (mean wear time 1354 minutes per day vs 1079 minutes per day, p = 0.001). A higher number of GENEActiv devices recorded valid data over the wear period, both at the minimum threshold (91.7% vs 75%) and higher threshold (75% vs 58.3%). A greater number of complete 24-hour wear periods were recorded within each 7-day period using the GENEActiv than the Actigraph device (5.1 vs. 3.7).

Table 12 *- Number of devices capturing data, including valid data, and total wear time by device*

	Actigraph	GENEActiv	p-value for difference
No. devices returned with any data captured (%)	9 (75%)	11 (91.7%)	0.197
Number of devices with minimum valid data* (%)	9 (75%)	11 (91.7%)	0.685
Number of devices with higher valid data† (%)	7 (58.3%)	9 (75%)	0.504
Number of full 24-hour periods recorded (S.D.)	3.7 (2.3)	5.1 (1.8)	0.150
Wear time/day – min (S.D.)	1079 (215)	1354 (102)	0.001

* More than 10 hours data for 2 weekdays and 2 weekend days

† More than 16 hours data for 2 weekdays and 2 weekend days

Despite the devices being worn over two separate periods, the average output from the devices across 24 hours (ENMO), during the least active 5 hours (L5) and most active 5 hours (M5) showed no significant differences between devices (Table 13). Time spent in MVPA, using both bout and non-bout criteria, was higher when measured by the GENEActiv devices compared with the actigraph devices. Although this was not statistically significant, the magnitude of difference between the two devices was large with over two hours more MVPA recorded by the GENEActiv device over the course of a week where participants had valid data for both

devices. In total, only three participants met World Health Organization (WHO) recommendations on time in MVPA per week according to 'bout' criteria ($MVPA_{10}$).

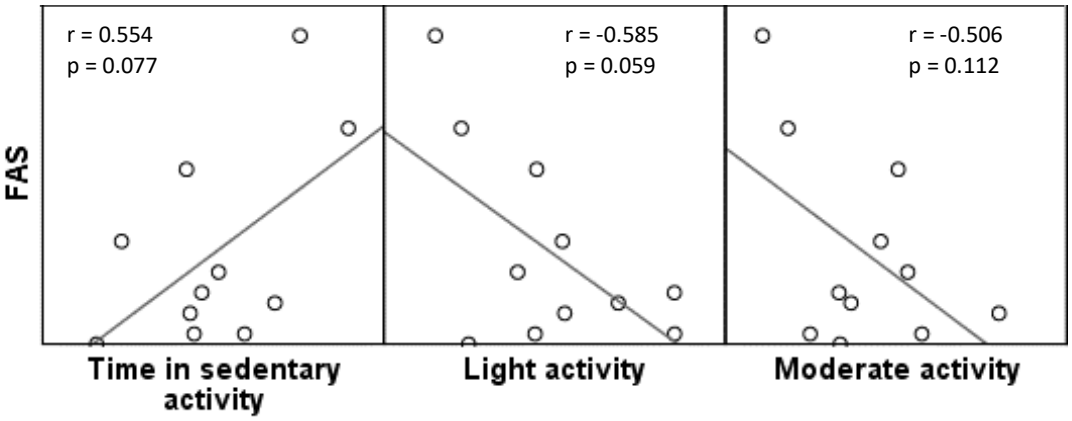
Table 13 *- Device outputs during wear periods*

	Actigraph	GENEActiv	Within-patient magnitude of difference*
ENMO – milli-g (S.D.)	25.7 (6.3)	27.4 (7.7)	1.24 (6.8)
L5 – milli-g (S.D.)	4.2 (2.7)	4.3 (2.2)	0.62 (1.8)
M5 – milli-g (S.D.)	48.5 (15.0)	51.3 (17.2)	3.19 (9.9)
MVPA (week) – min (S.D.)	556.9 (308.4)	668.1 (345.2)	148.2 (239.8)
$MVPA_{10}$ (week) - min (S.D.)	56.1 (62.0)	72.2 (74.8)	30.4 (38.2)

*Where paired data available; 8 participants provided data from both devices
ENMO – Euclidean Norm Minus One-g (mean accelerometer output over 24-hour period)
L5 – Mean accelerometer output (in milli-g) during the least active 5 hour period per day, averaged across all valid days
M5 - Mean accelerometer output (in milli-g) during the most active 5 hour period per day, averaged across all valid days
MVPA – Moderate or Vigorous Physical Activity using 100milli-g cut-off; no bout criteria used
$MVPA_{10}$ – Moderate or Vigorous Physical Activity using 100milli-g cut-off; bout criteria of 80% of any 10 minute block spent above 100milli-g threshold used

From the GENEActiv data, participants spent 427.3 minutes per day in sedentary behaviour; over half of their awake time. The mean time spent within each activity threshold per day were 245.4 minutes in light activity, 118.1 minutes in moderate activity and 7.1 minutes in vigorous activity, although the time in vigorous activity was skewed because of a high outlying value. With the outlying value removed the mean time spent performing vigorous activity fell to 3.1 minutes per day. Correlations between FAS scores and time spent within activity thresholds are shown in Figure 6. Moderately strong associations were seen between FAS scores and time in sedentary behaviours (r = 0.554, p=0.077), and time in light activity (r = -0.585, p=0.059). Weaker correlation was seen between moderate activity (r=-0.506, p=0.112) and FAS scores.

***Figure 6** - Correlation of Fatigue Assessment Scale score and time spent in activity thresholds from GENEActiv data*



3.4 Discussion

This study sought to clarify the preferred device by patients with sarcoidosis. A clear preference was demonstrated for the GENEActiv device, with the difference in scores on the VAS being statistically significant across all domains. Comments received from participants suggested they disliked the size and the strap of the Actigraph. The design of the GENEActiv appeared more comfortable, although feedback suggested that participants would have liked a watch face to negate needing to wear both a watch and the accelerometer. Overall, the GENEActiv appeared much less intrusive, with participants noting reduced awareness of the device with less interference with normal activity. This should provide a better reflection of daily activity through increased wear-time (which was seen in our results) and less disruption of normal daily activities. The high levels of wear time achieved from these devices is in keeping with benefits seen elsewhere; large population studies investigating activity, including the UK Biobank and NHANES, have switched from hip-worn accelerometers to wrist-worn devices due to increased wear time (260). Our results show that significant differences in wear time exist even within devices worn at the same location and reinforce the importance of choosing a device which is acceptable to the participants who will be wearing them.

The preferred device in this study, the GENEActiv, had a mean daily non-wear time of only 86 minutes per day averaged over the entire wear period. The ideal minimum wear time per day is debated with a number of different recommendations for valid wear time of accelerometers proposed. Our minimum validity definition (10 hours per day for two weekday and two weekend days) was taken from previous recommendations (261). Other reviews and studies have suggested that 13 hours (262) or 16 hours (255) are preferable to achieve an accurate picture of daily activity. Part of the rationale for these definitions was based on how sleep would impact on measurements due to difficulty separating sleep from periods of low activity (263). Modern accelerometry-based activity monitors, such as those tested here, incorporate additional sensors into the device (temperature and light sensing) which can be analysed with accelerometer outputs to determine sleep periods (264). These complex sensor arrangements allow sleep time and non-wear time to be excluded from activity analysis, meaning these devices can be truly "fit and forget" for participants in these trials. This also gives the option of collecting data on sleep patterns in addition to activity levels.

An exploratory analysis was performed to identify if there was a potential correlation between fatigue measured by FAS scores and time in activity thresholds. Previous studies looking at fatigue and sarcoidosis have used clinic-based measures of exercise capacity such as the six-minute walk test as predictors for fatigue, which have been shown to be poor at predicting fatigue scores (197, 265). Conversely, activity in free-living conditions was shown to be affected by fatigue in one study of patients with sarcoidosis (145). In the small number of participants monitored here, time spent in light activity showed moderate negative correlation with FAS scores. Additionally, time in sedentary behaviours, which has not previously been investigated, showed association with FAS scores. This suggests that changes in fatigue may be reflected in changes in activity and sedentary behaviours. Assessment of larger cohorts of patients with sarcoidosis will help to confirm these associations, as well as whether a relationship exists between fatigue and moderate or vigorous activity. Furthermore, investigation into whether increasing a patient's

activity levels reduces their fatigue scores could be made using devices such as the ones used here.

The strengths of this study include the wear-time required by each participant of the devices as well as the cross-over design which ensured that all subjects wore both devices for a period of time which would mirror the wear-time expected in future studies. This enables us to be confident that the GENEActiv would be more comfortable to wear, and therefore have greater wear time, when used in future studies to record activity patterns. The limitation of this study is the small number of participants. The number included was sufficient to determine a clear preference between the devices and therefore meet the primary objective, but this limits any conclusions beyond this. Determining the relationship between activity levels and patient-reported fatigue scores could not be accurately determined from the number of participants here, although this was not the purpose of the study.

3.5 Conclusions

The results of this study show a clear preference expressed by participants for the GENEActiv device. This stems from the improved comfort and reduced awareness of the GENEActiv compared with the Actigraph device. This in turn led to increased wear time and a greater amount of data being collected. As a clear preference was expressed for this device by participants, the GENEActiv device was therefore chosen for use in the FaST-MP study for measuring daily activity outcomes. The results may also influence device choice for future studies involving patients with sarcoidosis where outcomes of free-living activity levels are measured. Informed by the findings of this study, the next chapter of this thesis reports the full results of the FaST-MP study, including the activity outcomes measured using the GENEActiv devices piloted here.

Chapter 4: *Fatigue and Sarcoidosis – Treatment with Methylphenidate (FaST-MP) feasibility study methods*

Methods for *Fatigue and Sarcoidosis – Treatment with Methylphenidate (FaST-MP) feasibility study* published as:
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4.1 Introduction

Existing guidelines for managing sarcoidosis (83, 84) do not include advice on managing sarcoidosis-associated fatigue. In Chapter 2 the current lack of evidence for treatment options was described, although evidence for the use of neurostimulants, such as methylphenidate, was promising and required further exploration. Questions remain regarding how best to undertake a study of these agents; previous trials utilised a cross-over design, short study duration and measured primary outcomes using questionnaire-data. In the previous chapter a cross-over study of activity monitors determined the preferred device by patients with sarcoidosis. The results identified that the GENEActiv original wrist-worn device was preferred by patients, resulting in longer wear-times. This study was performed in preparation for a double-blind, parallel-arm feasibility study of methylphenidate for sarcoidosis-associated fatigue as one of the outcomes being tested is the practicality and reliability of using outputs from a wrist-worn activity monitor device as an outcome measure. The *FaST-MP* feasibility study is described in this chapter, determining the feasibility of recruiting and retaining participants as well as which outcome measures should be considered for any full phase III trial performed in the future.

Background

Methylphenidate (and its isomer dexmethylphenidate), which is used to treat attention deficit hyperactivity disorder (266), is a piperidine class stimulant which works by amplifying dopamine signals through inhibition of dopamine reuptake and enhancement of extracellular dopamine in the basal ganglia (267). The use of methylphenidate as a symptomatic treatment of sarcoidosis-associated fatigue has been suggested and trialled in a small study (173). However, that study only included ten participants, receiving medication for only eight weeks, and used a cross-over design which has been suggested to be inappropriate for trials investigating methylphenidate due to potential carry-over effects and difficulties with blinding within a cross-over study (233).

The drug has been used to treat fatigue in other settings with good effect. In a placebo-controlled, double-blind trial in post-chemotherapy participants with fatigue, methylphenidate exhibited a clinically significant reduction in fatigue (211). Prior to the results from that trial, a Cochrane review of treatments for cancer-related fatigue from five randomised controlled trials (RCTs) had shown an improvement in fatigue scores during methylphenidate treatment, leading the researchers to conclude "the current evidence supports the use of psychostimulants in cancer-related fatigue" (268). Another trial investigated methylphenidate for the treatment of fatigue in 109 HIV-positive patients over a 6-week period. Methylphenidate improved fatigue on a visual analogue scale, with a 26.2 point increase (maximum of 100) from baseline, and 41% of participants receiving the drug demonstrating a greater than 50% improvement in visual analogue scale score (213). In contrast, no difference between methylphenidate and placebo was seen in a cohort of 68 fatigued patients followed over a 12-week period who had received radiotherapy for brain tumours (212).

Rationale for a feasibility study

Prior to designing a definitive phase III study to determine the efficacy of methylphenidate for treating fatigue in sarcoidosis, issues around the feasibility of undertaking a sufficiently large trial need to be resolved. Completed trials have only used methylphenidate for 8-12 weeks, whether using it for sarcoidosis-associated fatigue or other causes of fatigue. Therefore, sustainability of effect, tolerability of medications over a longer period and retention of participants within the trial are unknown. Whilst medications such as methylphenidate may not be used on a continuous basis in the clinical setting, their use on a 6-12 month basis may not be unreasonable, hence the need to review the effect of the medication over a longer period. It is however unclear how many people would be willing to participate in a longer trial. It is also unclear how many potential participants would be suitable for enrolment using our present inclusion and exclusion criteria. For this reason, a feasibility trial is necessary before committing to a larger trial. Finally, whether a full phase III RCT is feasible is unclear; the potential difficulty in maintaining blinding for

both clinicians and patients due to clear clinical effect and characteristic adverse events may render a placebo-controlled study meaningless.

In addition to determining the feasibility of a larger trial, questions remain about whether recording of physical activity measures is useful and feasible within such a trial. Patients with sarcoidosis have been shown to have lower activity levels when fatigue is present (145) whereas 6MWT values have been shown not to change even when fatigue is treated (173) and the MSWT has not previously been trialled for this. The *FaST-MP* trial evaluates exercise capacity and physical activity using the modified shuttle walk test (MSWT) for exercise capacity and accelerometer-measured physical activity volume and intensity. Measuring exercise capacity in a laboratory setting is different to measuring daily physical activity levels in free living conditions. Factors other than physical capability can affect levels of activity, including social factors and volition. This trial will therefore evaluate the feasibility of using the GENEActiv original wrist-worn accelerometer, evaluated in the previous chapter, as an outcome measure in a clinical trial.

Objectives

The primary objective of this feasibility study was to determine the feasibility of conducting a large trial to investigate the clinical effectiveness of methylphenidate for the treatment of fatigue associated with sarcoidosis. Exploratory analysis of clinical outcomes is a secondary objective, although the study is not powered for these outcomes.

4.2 Methods

Trial design

This was a double-blind, placebo-controlled single-centre, randomised trial with a primary objective of determining the feasibility of performing a subsequent phase III study powered for clinical efficacy. Exploratory analysis of the clinical effect of methylphenidate on fatigue scores and health-related quality of life in patients with

sarcoidosis was undertaken using the data collected. The trial allowed up to thirty participants to be randomized in a 3:2 ratio to receive methylphenidate or placebo for up to 24 weeks. The asymmetrical allocation was chosen to increase the number of participants receiving methylphenidate, increasing the data collection on side effects and drug tolerability.

At the end of the study three audio-recorded, moderated focus groups, with purposive sampling to select patients with different baseline characteristics and response to therapy were undertaken to refine the understanding of the results and inform the design of any future definitive study. This was an optional additional part of the study and participants were asked to give their consent to participate in these focus groups. Participants were still able participate in the clinical trial even if they did not wish to participate in the focus groups.

Study setting

The study was undertaken at the Norfolk and Norwich University Hospital (NNUH; Norwich, Norfolk), a regional tertiary centre for patients with interstitial lung diseases (ILD). All study visits and activities took place within the NNUH. Patients were recruited from the respiratory department of the NNUH. In addition, patients could be recruited from other hospitals in the East of England if they were (a) willing to travel to the NNUH for the planned study visits and (b) their primary physician at their treating hospital was agreeable for them to participate in the study.

Participants

Sample size

A target sample size of 30 participants was judged to be reasonable at a single site responsible for the care of approximately 300 patients with sarcoidosis through the respiratory medicine department, although a minimum target of 20 participants

was specified to estimate feasibility outcomes (269). Subsequent review of enrolment after four months showed that recruitment had been slower than expected. The ability to recruit centres as Participant Identification Centres (PICs) was added in a major amendment in April 2017 to facilitate increased recruitment; two centres (Papworth Hospital, Cambridgeshire and Addenbrooke's Hospital, Cambridge) were approved as PICs during the study. All research activities beyond participant identification occurred at NNUH exclusively.

The change in FAS score from baseline gave an estimate of effect size; this informed sample size requirements for any future phase III study. The number and proportion of participants recruited and retained within the study enabled an estimate of the number of additional participants required to cover for withdrawals during a future study. An estimated minimum retention rate of 60% of participants over the longer 24-week study duration was considered the minimum number to suggest a future study would be feasible over this duration.

Eligibility criteria

Participants were considered eligible for enrolment in this trial if they fulfilled all the inclusion criteria and none of the exclusion criteria as defined below.

Participant inclusion criteria

1. A proven diagnosis of sarcoidosis – this was defined as either a biopsy-proven disease (non-caseating granulomas from a tissue biopsy), or a diagnosis of sarcoidosis agreed by an interstitial lung disease multidisciplinary team (ILD MDT) meeting.
2. Stable disease (treatment unchanged for 6 weeks, without anticipation of change in treatment during trial period)
3. Able to give informed consent
4. Participant-reported fatigue and FAS score greater than 21 units (defined cut off for significant fatigue (270))

Participant exclusion criteria

1. Evidence of co-existing obstructive sleep apnoea. Patients were screened with the "STOP-Bang" questionnaire; those with a score of greater than 4 were required to undertake overnight oximetry. Participants were excluded if overnight oximetry revealed a desaturation index of more than 15 events per hour. Below this, participants were eligible for inclusion.
2. Documented history of significant cardiac disease (including cardiac sarcoid) OR associated disease which would increase risk of underlying coronary artery disease (cerebrovascular disease, previous stroke or peripheral vascular disease). Definitively treated cardiac disease e.g. previous myocardial infarction treated with stents or coronary artery bypass grafting with no ongoing symptoms was permitted.
3. Abnormal thyroid function (hyper or hypothyroidism) defined as abnormal screening thyroid function tests (Thyroid stimulating hormone (TSH) outside normal range of 0.35 – 3.50 mU/L or thyroxine (T4) outside normal range of 8 – 21 pmol/L).
4. History of seizures, excluding febrile convulsions whilst an infant.
5. Abnormal electrocardiogram (ECG) with evidence of arrhythmia (except first degree heart block which has been stable for 3 months).
6. Concomitant therapy with any of the following drugs:
    a. Tricyclic anti-depressants (amitriptyline, clomipramine, dosulepin, doxepin, imipramine, lofepramine, nortriptyline, trimipramine, mianserin, trazodone)
    b. Monoamine oxidase inhibitors (phenelzine, isocarboxazid, tranylcypromine, moclobemide, selegiline)
    c. Buprenorphine
    d. Tramadol
    e. Levodopa
    f. Clonidine
    g. Methylene blue
    h. Warfarin

   i. Antipsychotics, both typical and atypical
   j. Decongestants (phenylephrine, ephedrine, pseudoephedrine and others).
7. Glaucoma or raised intra-ocular pressure for any reason.
8. Patients with established liver disease defined as Child-Pugh class B or C.
9. Documented medical history of psychiatric disorders (excluding depression)
10. History of drug-dependence or addiction at any time
11. Female participant who was pregnant, lactating or planning pregnancy during the course of the trial
12. Female patient of childbearing potential who was unable or unwilling to take two acceptable forms of contraception (see below)
13. Any patient receiving an investigational drug or biological agent within 6 weeks (or five times the half-life if this is longer) prior to study entry.

Exclusion criteria on pregnancy

Female patients of childbearing potential were required to use contraception due to the theoretical risk of teratogenicity, growth retardation and premature birth with methylphenidate use in pregnancy. Those unable or unwilling to take two of the following acceptable methods of contraception for the duration of their treatment were excluded from participating in this trial:

1. Established use of oral, injected or implanted hormonal methods of contraception
2. Intra-uterine device (coil)
3. Barrier methods of contraception (condom or occlusive cap with spermicide – *use of spermicide without a form of barrier contraception was **not** considered an acceptable form of contraception)*
4. Alternatively, absolute and continuous abstinence was acceptable. *Periodic abstinence (calendar, ovulation, symptothermal, post-ovulation) or withdrawal were **not** considered acceptable methods of contraception*

For the purposes of this trial the definition of a woman of childbearing potential was a sexually mature woman (i.e. has experienced menstruation) who has not been postmenopausal for 12 consecutive months (i.e. who has had menses at any time in the last 12 months without an alternative medical cause).

Permitted treatments and concomitant care

Patients were permitted to receive any treatment for their sarcoidosis. Potential treatments included prednisolone, methotrexate, azathioprine, mycophenolate, hydroxychloroquine or infliximab. These treatments were required to be at a stable dose (i.e. no plan to wean down or increase dose during the trial period) for at least 6 weeks prior to screening for enrolment in the trial. All concomitant medication was recorded at baseline and changes to concomitant medication were recorded at each visit.

Patients receiving selective serotonin reuptake inhibitors (SSRIs) were permitted to enter the trial. Previous trials have used methylphenidate to attempt to enhance the effectiveness of SSRIs, including doses of methylphenidate greater than the maximum daily dose prescribed within this study. The side-effect profile when using these drugs together appeared safe, with no significant differences in side-effects or drop outs compared with placebo in one trial of 142 elderly patients (271).

Participant identification, recruitment and retention

Participant identification

Patients were identified by review of ILD MDT meeting minutes or summaries, screening patient registries, hospital medical records, a locally-held and maintained database of patients interested in research, or clinical details. This occurred at the NNUH. PIC sites were able to identify additional potential participants and inform the study team at the NNUH but were not required to screen their entire sarcoidosis patient population.

Patients at the NNUH who were identified through any of these methods as potential candidates had a retrospective case review to determine whether they met inclusion criteria 1 and 2. Patients who met inclusion criteria 1 and 2 who did not obviously meet any exclusion criteria at pre-screening were approached with the permission of their primary respiratory physician. Participants referred from PIC sites were contacted by phone to check eligibility, with additional data to confirm their diagnosis sought from their treating hospital. The data was collected using an anonymised form. The data captured consisted of: Patient demographics (age, sex, race, BMI), most recent lung function, duration of disease, current treatment and duration of treatment, organs affected by sarcoidosis and medical history.

Participant recruitment

Recruitment strategies included any of the following:

- Patients could be approached by their clinical care team directly when they attend the hospital outpatient clinic. They received an invitation letter on hospital headed paper which provided an overview of the study and the patient information sheet. The research team contacted the patient by phone 3-7 days later if they had given their usual team permission to be contacted.
- Alternatively, the clinical team could post an invitation letter, with or without a patient information sheet, with a reply form detailing a range of methods for the interested potential patients to contact the research team. This method was used to contact patients identified either through the ILD team (clinic or MDT), or patients who are on the research participant database held by the respiratory research group at the NNUH.
- Where patients were due to attend clinic for a routine appointment in the near future, the clinical care team could mail an invitation letter on hospital headed paper, providing an overview of the study, and a patient information sheet, so that the patient received these documents at least 24 hours in advance of their routine clinic assessment visit. This enabled consent to be sought during their attendance at clinic.

- Posters advertising the trial were placed in the respiratory department at the NNUH, including contact details for patients interested in the trial.
- Patients who were identified at PIC sites rather than the Norfolk and Norwich University Hospital were sent a PIS by the research team in Norwich after their details had been passed on by their primary physician from their hospital. Consent was taken at the Norfolk and Norwich University Hospital.

Potential patients could be contacted by phone between 3 and 7 days after the mailing of the letter to ensure that they had received it.

Participant consent

Consent was obtained prior to any study related procedure. Following consent, screening bloods were taken and other eligibility criteria were assessed. Patients meeting all entry criteria (after review of screening tests) were only randomised prior to their baseline visit (visit 0) once all inclusion and exclusion criteria had been checked. A two-week period between consent (at the screening visit) and commencing medications (at visit 0) allowed a cooling-off period for participants; consent was checked at visit 0. At the same time as confirming consent, a declaration of understanding was signed by the participant to confirm willingness to receive the medications at the dose prescribed and not to give away or sell their medications. Following this, medication was dispensed by hospital pharmacy to the study team, who would give the study medication directly to the participant at their study visit.

Participant retention

Participants who discontinued protocol treatment, for any reason, were asked to remain in the trial for the purpose of follow up and data analysis. Although not obliged to give a reason for discontinuing their trial treatment, a reasonable effort was made to establish this, whilst remaining fully respectful of the participant's rights.

Interventions

Active treatment arm

The intervention under investigation was methylphenidate hydrochloride (*Tranquilyn*), which was manufactured for this study in 10mg tablets with over-encapsulation by a gel capsule. The drug supply was produced by Guys and St Thomas' Pharmacy Manufacturing Unit. Participants commenced at 10mg of methylphenidate hydrochloride (one capsule) twice daily, increasing to 20mg (two capsules) twice daily after two weeks. Participants continued the medication for up to 24 weeks in total; participants on the higher dose (20mg twice daily) received an additional two weeks supply of the lower dose (10mg twice daily) for 2 weeks following completion of the trial to minimise the risk of any withdrawal symptoms.

Comparator arm

The comparator arm for this study was an identical placebo capsule; the placebo was manufactured at Guys and St Thomas' Pharmacy Manufacturing Unit. Participants in the placebo arm commenced medications at one capsule twice daily, increasing to two capsules twice daily after two weeks if the medication had been tolerated. Participants receiving two capsules twice daily at the end of the 24-week treatment period were reduced to one capsule twice daily and then discontinued the trial medications at the end of this period.

Dispensing schedule

Participants received sufficient investigational medicinal product (IMP) for them to take their prescribed dose until their next study visit. This was dispensed at two-weekly intervals for the first 6 weeks, then a six-week supply of IMP dispensed at 6, 12 and 18-week visits. All medication was dispensed from the pharmacy at the NNUH. The IMP was dispensed in bottles of 28 capsules. Assuming a participant was uptitrated to the higher dose (20mg twice daily) after two weeks and maintained

this dose through the study, the participant received the following quantities of IMP at each visit:

- 1 bottle (28 capsules) at visit 0 (0 weeks)
- 2 bottles (56 capsules) at visits 1 and 2 (2 and 4 weeks)
- 6 bottles (168 capsules) at visits 3, 4 and 5 (6, 12 and 18 weeks)
- 1 bottle (28 capsules) at visit 6 (24 weeks)

Treatment modifications, interruptions and discontinuation

The dose was down-titrated in the event of side effects at the higher dose (20mg/2 tablets twice daily). In the case of side effects, the dose was reduced to 10mg (1 tablet) twice daily. In the event of any side effects whilst receiving 10mg (1 tablet) twice daily the treatment was discontinued. Once a patient had a dose reduction no re-escalation was permitted, even if the adverse event leading to the reduction resolved.

At the completion of the trial (week 24) participants on 20mg twice daily reduced to 10mg twice daily for two weeks to reduce the risk of withdrawal symptoms before discontinuing IMP completely.

Side effects which may lead to down-titration of the drug were:

1. Nervousness or restlessness
2. Nausea, indigestion
3. Nasal stuffiness
4. Tachycardia (resting HR >100 which had not been observed at lower dose)
5. Cough
6. Arthralgia
7. Anorexia
8. Participant choice

Participants discontinued the study drug **immediately** (regardless of dose) in the case of the following events:

1. Intolerance to study drug due to development of clinical side effects
2. Generalised rash and pruritis
3. Abnormality of follow-up ECG (arrhythmia, severe tachycardia (>120bpm) or conduction abnormality)
4. Development of palpitations or chest pain
5. Development of severe anxiety or euphoria, personality change or abnormal/bizarre behaviour, or other psychiatric disease
6. Development of seizures or other neurological problems
7. Development of severe hypertension (BP >180mmHg on two separate occasions or symptoms of malignant hypertension, notably severe headache, blurred vision or seizure)
8. Failure to take the medication as directed or overdose of study medication
9. Change in liver function tests (raised ALT >3x upper limit of normal) or deterioration in renal function (eGFR <30ml/minute/1.73m2)
10. Inter-current illness that prevents further treatment
11. Any change in the participant's condition that in the clinician's opinion justifies the discontinuation of treatment
12. Withdrawal of consent for treatment by the participant

Participants within the trial who required increases in their usual treatment for sarcoidosis were permitted to remain in the trial if both the patient's primary physician and the trial physician were in agreement. Any changes to sarcoidosis treatment or evidence of increased disease activity were recorded.

Assessments and outcomes

Feasibility outcomes

The primary outcomes were chosen specifically to determine the feasibility of a future phase III study investigating the clinical efficacy of neurostimulant medications for treatment of sarcoidosis-associated fatigue. Each primary outcome below is followed by the specific question which the outcome point aimed to answer.

1. Number of potential participants excluded *(how many patients with sarcoidosis are eligible?)*
2. Reason for exclusion from the study *(as above, as well as generalisability of the results – is the population included and continuing the trial representative?)*
3. Number of eligible participants agreeing to participate *(willingness of patients to participate)*
4. Recruitment rate *(how many centres would need to be involved?)*
5. Retention of participants and reason for withdrawal *(how many additional participants would be needed to ensure statistical power is maintained allowing for drop-outs?)*
6. Number of participants suffering side-effects or requiring reduction of methylphenidate dose due to emergence of side effects, and the dose most frequently tolerated by participants *(see assessment of safety below)*
7. Sustainability of effect (does a future trial need to be as long or is 8-12 weeks acceptable?)
8. Number of missed or unfilled assessments *(can accurate data be collected to capture the information required?)*
9. Number of patients correctly using accelerometers *(will patients remember to use the accelerometers for the required minimum four days out of the seven-day period?)*
10. Accuracy of predicting allocation to active or placebo arm at the end of the study by assessor and participant *(is blinding broken through participants determining which group they have been allocated to during the study from clinical effects or side-effects?)*
11. Acceptability of number of study visits and assessments *(does the study design deter participants?)*
12. Acceptability of randomization *(does the risk of only receiving placebo deter participants?)*
13. Acceptability of receiving a controlled drug *(is the choice of intervention acceptable to participants?)*
14. Compliance with medications *(how many doses are missed?)*

15. Mean change in fatigue score and standard deviation of change *(for power calculations; more detail is contained in the secondary outcomes section)*
16. Patient perception of participating in this trial *(through the use of focus groups)*

Secondary outcomes

In addition to the primary outcome measures listed above, an exploratory analysis of clinical measures was undertaken, covering participant-reported fatigue scores, depression scores, health-related quality of life, healthcare utilisation, physical capacity and activity and sleep quality. The specific outcome measures used, including the rationale for their use, are described below:

Questionnaires

Questionnaires were administered at each participant's visit, with data checking at the time to minimise the risk of missing values. The final set of questionnaires, performed 6-8 weeks following the completion of study medications, was completed by the participant at home whereby postal questionnaires were sent to the participant and returned via pre-paid envelope.

1. Fatigue was assessed using two separate questionnaires; the FAS (112) and FACIT-Fatigue (272). The FAS is a ten-question instrument with a maximum score of 50 points and a known MCID of four points; higher scores indicated greater fatigue (270) (22). The FACIT-Fatigue is a generic fatigue scale with 13 items. Lower scores indicate greater fatigue. The measurement properties of both these instruments is discussed in chapter 1, section 1.9.
2. Disease specific health related quality of life was assessed using the King's Sarcoidosis Questionnaire (KSQ) (273). This is the only validated disease-specific health related quality of life tool for sarcoidosis, which was developed with cohorts of sarcoidosis patients in the UK. It calculates health status scores related to sarcoidosis activity and also includes a visual

analogue scale to report severity of cough. Results are reported for different sub-scales of disease-related symptoms (general health status, lung symptoms, eye symptoms, skin symptoms and medication-related problems) and an overall score (composite score) incorporating all sub-scale values. Lower scores for each subscale indicate greater problems.

3. Anxiety and depression were assessed using the Hospital Anxiety and Depression Score (HADS) (274). This 14-item questionnaire includes subscales for anxiety and depressive symptoms (HADS-A and HADS-D), with each item scored out of three. Total scores are out of 21 for each subscale, with a score >10 points indicating the presence of significant anxiety or depressive symptoms. Previous data have suggested that depression scores have improved with changes in fatigue scores (173).
4. Generic quality of life was assessed using EuroQoL-5D-5L (EQ5D) and SF-36 questionnaires. The EQ5D is a 2-page self-administered questionnaire (275), and was used to generate health utility values from the reported health states within the questionnaire. The SF-36 questionnaire consists of 36 items measuring various aspects of quality of life. It is one of the most frequently used patient-reported outcome measures across many different health conditions (276), and has been shown to correlate with fatigue scores in sarcoidosis patients (277); the results from the SF-36 were converted into short form 6-dimension (SF-6D) health states and then into health utility values.
5. Health and social care resource utilisation were captured through a custom-designed costs questionnaire. This included a baseline socioeconomic questionnaire and 3-monthly resource use questionnaires that captured details of medical contacts, carers and out of pocket patient expenses. This questionnaire was developed from tools within the Medical Research Council project “Database of instruments for resource-use management” (278). The tool was piloted within this study to determine whether it is appropriate for future use.
6. Sleep quality was measured using the Pittsburgh Sleep Quality Index (PSQI), a validated questionnaire for evaluating sleep quality (279, 280), to

determine if sleep quality is impacted by taking methylphenidate. This outcome was added during an amendment to the study made in April 2017 due to several participants reporting a subjective improvement in sleep quality whilst receiving medications.

7. An exit questionnaire (contained in appendix 5), asking whether a participant would want to continue the study medication if this were an option, was administered at week 24 or at the point of withdrawing from the study – these findings were complementary to the focus groups and assist with the feasibility outcomes.

Exercise and activity

Both physical capability and activity levels during free-living conditions were measured during this study, each recorded at 0, 12 and 24 weeks.

8. Measurement of physical capability was undertaken using the modified incremental shuttle walk test (MSWT) (281). This modification of the incremental shuttle walk test has been shown to strongly correlate with peak VO_2 levels when compared with cardiopulmonary exercise testing in sarcoidosis patients (240). It allows those with minimal cardiopulmonary impairment to be adequately stressed. This provides benefit over a 6MWT; methylphenidate has not been shown to significantly improve 6MWT measurements (173). This may be because as a self-paced test it is a sub-maximal exercise test – this has been shown to be the case in a study of ILD patients (including sarcoidosis) where peak oxygen uptake, CO_2 uptake and ventilation were all lower during 6MWT than on cardiopulmonary exercise testing (282). Using the MSWT overcomes these limitations.
   The test was performed on a 10 metre track, with two cones spaced 0.5 metres short of each end of the course, which the participant walked around to travel 10 metres per shuttle, in line with instructions for the test (240). Two assessors were present to confirm that the correct number of shuttles was reported and to provide support in the event of difficulties.

9. Measurement of physical activity was undertaken using wrist-worn GENEActiv Original (Activinsights, Cambridgeshire, UK); these are the devices piloted in the previous chapter.
   A device was worn for three 7-day periods; at the beginning of the study (prior to any medications), at 12 weeks +/- 2 weeks, and within 2 weeks of the end of the study (24 weeks).

Safety assessment

Documentation of any adverse event occurred at each visit. In addition, a clinical assessment was undertaken at each visit to seek and identify any adverse effect or concern about patient safety. Participant reported problems/side effects were recorded to collect safety data regarding extended use of methylphenidate in a sarcoidosis population. The following were recorded:

1. Number and severity of adverse events recorded during the trial.
2. Number of participants that developed ECG abnormalities during the trial.
3. Number of participants that developed abnormalities on blood tests (liver function, kidney function) and required discontinuation of the trial.

Participant timeline

A participant going through the trial was seen or contacted at the following time-points:

1) **Screening visit** (Visit (-1)); two weeks before starting medication
2) **Baseline visit at week 0** (Visit (0)); 2-week drug supply dispensed
3) **Phone call at week 1** (check for adverse events)
4) **Visit 1 at 2 weeks;** Safety measures and uptitration if appropriate, 2-week drug supply
5) **Phone call at week 3** (check for adverse events)
6) **Visit 2 at 4 weeks**; Safety measures, 2-week drug supply

7) **Phone call at week 5** (check for adverse events)
8) **Visit 3 at 6 weeks;** Safety and clinical measurements, 6-week drug supply
9) **Phone call at week 8** (check for adverse events)
10) **Phone call at week 10** (check for adverse events)
11) **Visit 4 at 12 weeks;** Safety and clinical measures, including measurements of activity and exercise, 6-week drug supply. Participants randomised after 02/02/2018 discontinue study medications after this visit.
12) **Phone call at week 14** (check for adverse events)
13) **Phone call at week 16** (check for adverse events)
14) **Visit 5 at 18 weeks;** Safety and clinical measures, 6-week drug supply. Participants randomised between 01/12/2017 and 02/02/2018 discontinue study medications after this visit.
15) **Phone call at week 20** (check for adverse events)
16) **Phone call at week 22** (check for adverse events)
17) **Final study visit at 24 weeks;** Clinical measurements, including measurements of activity and exercise.
18) **Questionnaires measured at 30 weeks** (sent by post and returned via post)
19) **[OPTIONAL] Focus group discussion regarding trial participation experience** (at least 6 weeks after finishing the study)

In total, participants were required to attend eight visits across the 24-week trial period, plus one optional extra visit for the focus group discussions, and they also received nine phone calls from the study team. The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) diagram overleaf (Table 14) summarises the study visits and the assessments made at each one, although the diagram does not show the planned phone calls participants received at week 1, 3, 5, 8, 10, 14, 16, 20 and 22.

***Table 14** – SPIRIT diagram of events occurring within the FaST-MP trial*

	Enrolment	**Allocation**	**Post-allocation**						**Close-out**
TIMEPOINT	*-2 weeks*	0 weeks	*2 weeks (+/- 3 days)*	*4 weeks (+/- 3 days)*	*6 weeks (+/- 3 days)*	*12 weeks (+/- 1 week)*	*18 weeks (+/- 1 week)*	*24 weeks (+/- 1 week)*	*+4-8 weeks*
ENROLMENT:									
Eligibility screen	X	X							
Informed consent	X								
Allocation		X							
Declaration of understanding (prior to receiving IMP)		X							
INTERVENTIONS:									
Methylphenidate (X = uptitrate dose) (O = drug dispensed)		O	O X	O	O	O	O		
Placebo (X = uptitrate dose) (O = drug dispensed)		O	O X	O	O	O	O		
ASSESSMENTS:									
Safety bloods (FBC/LFT/U+Es)	X		X	X	X	X			
Safety questionnaire		X	X	X	X	X	X		
Pregnancy test	X	X							
ECG	X		X	X	X	X		X	
Spirometry		X				X		X	
Modified Shuttle Walk Test		X				X		X	
Accelerometer (7 days)	X					X		X	
QUESTIONNAIRES:									
- FAS	X	X	X	X	X	X	X	X	X
- FACIT-F		X	X	X	X	X	X	X	X
- HADS		X			X	X	X	X	X
- Short Form-36		X			X	X	X	X	X
- EQ5D		X			X	X	X	X	X
- KSQ		X			X	X	X	X	X
- Costs		X				X		X	
- PSQI		X				X		X	X
- Exit Questionnaire								X	
Focus group (post-trial)									X

The timeline shows the study visits for participants recruited prior to 01/12/2017. Due to a lower than anticipated recruitment rate, participants entering the study after 01/12/2017 received a reduced period of study medication. Participants randomised between 02/12/2017 and 12/01/2018 received study medications for 18 weeks, and discontinued the study medication at visit 5. Participants randomised between 13/01/2018 and 02/03/2018 received study medications for 12 weeks and discontinued the study medication at visit 4. In both cases, participants still completed postal questionnaires six weeks after completing study medications. This amendment was made to increase recruitment time and maximise participation in the study.

Assignment of intervention

Allocation sequence generation

The allocated treatment for a patient was generated via computer-written code. A randomisation sequence with a 3:2 ratio in favour of methylphenidate was generated. Allocation was determined based upon block randomisation using blocks of five with stratification by severity of fatigue (FAS 22-34 and FAS 35-50). No other factors were used to adjust randomisation given the single-centre nature, small number of participants included and primary objective of assessment of feasibility. The randomisation sequence was generated by a statistician within Norwich CTU.

Randomisation method and concealment

Allocation (randomisation) was performed by a process embedded in a web-based data management system. This was designed using REDCap, a secure web-application for managing databases. The randomisation code was saved in the study database for emergency unblinding purposes. When a patient was randomised, the database automatically generated and sent an e-mail to the NNUH trial pharmacy to allow medication dispensing. Within the pharmacy, labels identifying group were used, with the group identifier then removed before medication was dispensed. This

system enabled blinding of the research team and participants during randomisation and medication dispensing.

Blinding

This was a double-blind study. The placebo and active treatments appear identical and were dispensed in identical containers. All trial patients, care providers, outcome assessors and data analysts remained blind to treatment throughout the study. The trial pharmacists at the NNUH were aware of the treatment group due to unequal arm size; they did not disclose the group allocation to any of the trial team and medication labels did not reference the group to which the participant was allocated; this data was contained on a tear-off strip which was removed prior to dispensing to the study team. During study monitoring and auditing, pharmacy monitoring was performed by a member of staff from the clinical trials unit; this ensured no member of the clinical or trial team within the NNUH was unblinded throughout the study.

Emergency unblinding

In the event of any of the following events, it was permitted for unblinding of an individual's allocated treatment to be performed:

· To enable treatment of severe adverse event/s, or

· In the event of an overdose

Where possible, requests for emergency or unplanned unblinding of individuals were made via the trial manager and agreement of the Chief Investigator was then sought. However, in circumstances where there was insufficient time to make this request or for agreement to be sought, it was possible for the treating clinician to request that the participant's allocation was unblinded. The chief investigator was then required to authorise this, which could then be done through the REDCap research database. In the event of unblinding, it was required that the details of the request and the individuals alerted to the allocation be recorded and reported to Norwich Clinical Trials Unit (NCTU) by the chief investigator, including the identity of all recipients of the unblinding information.

Data management

Data was entered into the approved *FaST-MP* database by a member of the trial team. Participants were given a unique trial Participant Identification Number (PIN). Data was entered under this identification number onto the central database stored on the servers based at NCTU. The database was password protected and only accessible to members of the trial team, as well as external regulators if requested.

The identification, screening and enrolment logs, linking participant identifiable data to the pseudoanonymised Participant Identification Number (PIN), were held locally by the trial site in the form of a written case report form held alongside clinical notes in a locked filing cabinet within the respiratory research department at the NNIJH.

At the end of the study, following entry of the last data, the database was locked and underwent data verification; this entailed a review of 10% of the data points compared with the paper case report forms and questionnaires to ensure data accuracy. Following data verification, the data were unblinded for analysis.

Data monitoring and trial oversight

Trial steering committee

An independent trial steering committee (TSC) was convened to be responsible for the oversight of the trial, including safeguarding the interests of trial participants. The TSC provided guidance to the chief investigator (CI) and the sponsor on all aspects of the trial through the independent chairperson. A terms of reference document was drafted to specify the membership, activities, and authority, which all members of the TSC were required to approve and sign. Meetings of the TSC occurred every six months whilst the trial was open, with a final meeting once the trial was closed and analysed. A total of four meetings were held.

Safety committee

A safety committee (SC) monitored adverse events occurring within the trial. This was convened rather than a full Data Monitoring and Ethics Committee (DMEC) due to the small nature of the study. The SC met every six months (three meetings were held in total) and reviewed the adverse events that were reported by each participant. The SC were provided with the allocation group for each participant to aid their decision making; no member of the trial team was present during this part of the SC meeting to avoid unblinding.

Following each SC meeting, which took place one month prior to each TSC meeting, a report was generated for the TSC stating their assessment of whether the trial should be allowed to continue.

Safety Reporting

Definitions

Definitions of harm from the EU directive 2001/20/EC Article 2 were used for this trial. The definitions of adverse events are shown in table 15. All adverse events were assessed for the strength of causal relationship between the study medication and each event. The definitions used for assessment of these relationships are shown in table 16.

***Table 15** - Definitions of harm, adapted from EU directive 2001/20/EC Article 2*

Definition	Description
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this product.
Adverse Reaction (AR)	Any untoward and unintended response within a participant to the investigational medicinal product related to any dose administered.
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the summary of product characteristics (SPC).
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)	Any AE or AR that at any dose: • results in death • is life threatening • requires hospitalisation or prolongs existing hospitalisation • results in persistent or significant disability or incapacity • is a congenital anomaly or birth defect • or is another important medical condition Life threatening refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that might hypothetically cause death if it was more severe. Hospitalisation is defined as a non-elective in-patient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the Summary of Product Characteristics (SmPC).

***Table 16** - Causality definitions*

Relationship	Description
Unrelated	There is no evidence of any causal relationship
Unlikely to be related	There is little evidence to suggest that there is a causal relationship or there is another reasonable explanation for the event
Possibly related	There is some evidence to suggest a causal relationship. However, the influence of other factors may have contributed to the event.
Probably related	There is evidence to suggest a causal relationship and the influence of other factors is unlikely
Definitely related	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

Capturing safety data

Adverse events for each participant were captured from the date of the first dose of study medications until 30 days after the last treatment dose (as per the research study protocol). Events occurring between consent and the first administered dose were not recorded as AEs as the participant had not been exposed to treatment beyond normal care.

For each participant an AE form was kept, recording each AE experienced during the study. Each event recorded a description of the medical problem, the severity of the event defined using the Common Terminology Criteria for Adverse Events (CTCAE) v4.0 grading, assessment of relationship to the study medication, action taken (none, medication temporarily stopped, medication permanently stopped) and outcomes. Events were recorded at each follow-up visit and phone call, or recorded when brought to the attention of the investigators if the participant contacted the study team between scheduled visits.

Adverse event reporting

All SAEs were reported to NCTU and the NNUH Research and Development office within 24 hours of the trial team becoming aware of the event. For each event occurring, a report was completed including an assessment of the relationship between study medication and the event to determine if the event was an SAE, SAR or SUSAR. Any participant suffering an SAE, SAR or SUSAR was followed up until clinical recovery was complete or the event had stabilised, with follow-up forms completed and returned to NCTU to provide further information as it became available.

NCTU was delegated the duties of reporting SUSARs and other SARs. Any fatal or life-threatening SUSAR experienced during the study was required to be reported to regulatory authorities (MHRA) within seven days of NCTU becoming aware of the event; for all other SUSARs, events had to be reported within 15 days.

Expected adverse events with Methylphenidate

The summary of product characteristics (SmPC) document for Methylphenidate Hydrochloride (*Tranquilyn*) 10mg tablets lists the potential adverse events that have been reported during clinical trials and post-market spontaneous reports for this medication and other methylphenidate hydrochloride formulations. The expected adverse drug reactions documented in the SmPC are summarised in Table 17, including the estimated frequency of event occurrence.

***Table 17** - Frequency estimates of adverse drug reactions for methylphenidate hydrochloride*

Frequency	Adverse event
Very common *(≥1 in 10)*	Insomnia, nervousness; Headache.
Common *(≥1 in 100, <1 in 10)*	Naso-pharyngitis; Anorexia, decreased appetite; Affect lability, aggression, agitation, anxiety, depression, irritability, abnormal behaviour; Dizziness, dyskinesia, psychomotor hyperactivity, somnolence; Arrhythmia, tachycardia, palpitations; Hypertension; Cough, pharngolarygeal pain; Abdominal pain, diarrhoea, nausea, stomach discomfort and vomiting (usually occur at start of treatment and are alleviated by concomitant food intake), dry mouth; Alopecia, pruritis, rash, urticaria; Arthralgia; Pyrexia; Changes in blood pressure and heart rate (usually an increase), weight decreased.
Uncommon *(≥1 in 1000, <1 in 100)*	Hypersensitivity reactions, anaphylactic reactions, auricular swelling, bullous conditions, exfoliative conditions, urticarias, pruritis, rashes and eruptions; Psychotic disorders, auditory, visual and tactile hallucinations, anger, suicidal ideation, mood alteration, mood swings, restlessness, tearfulness, tics, worsening of pre-existing tics, hypervigilance, sleep disorder; Sedation, tremor; Diplopia, blurred vision; Chest pain; Dyspnoea; Constipation; Hepatic enzyme elevations; Angioneurotic oedema, bullous conditions, exfoliative conditions; Myalgia, muscle twitching; Haematuria; Chest pain, fatigue; Cardiac murmur.
Rare *(≥1 in 10,000, <1 in 1000)*	Mania, disorientation, libido disorder; Difficulties in visual accommodation, mydriasis, visual disturbance; Angina pectoris; Hyperhidoriss, macular rash, erythema; Gynaecomastia.
Very rare *(≤1 in 10,000)*	Anaemia, leucopenia, thrombocytopenia, thrombocytopenic purpura; Suicidal attempt, transient depressed mood, abnormal thinking, apathy, repetitive behaviours, over-focussing; Convulsions, choreo-athetoid movements, reversible ischaemic neurological deficit, neuroleptic malignant syndrome; Cardiac arrest, myocardial infarction; Cerebral arteritis and/or occlusion, peripheral coldness, Raynaud's phenomenon; Abnormal liver function, including hepatic coma; Erythema multiforme, exfoliative dermatitis, fixed drug eruption; Muscle cramps; Sudden cardiac death; Blood alkaline phosphatase increased, Blood bilirubin increased, platelet count decrease, white blood cell decrease.
Not known (cannot be estimated from the available data)	Pancytopenia; Delusions, thought disturbances, confusional state, logorrhoea; Cerebrovascular disorders (including vasculitis, cerebral haemorrhages, cerebrovascular accidents, cerebral arteritis, cerebral occlusion), grand mal seizures, migraine; Supraventricular tachycardia, bradycardia, ventricular extrasystoles, Extrasystoles; Erectile dysfunction; Chest discomfort, hyperpyrexia.

Data Analysis

Primary outcomes (feasibility)

Primary data analysis assessed the feasibility outcomes described in *primary outcomes*. A screening log was maintained of all patients reviewed against the study eligibility criteria, including patient demographics and reason for exclusion. A second screening log was kept of eligible patients contacted for the study. The results of both logs were presented as a Consolidated Standards of Reporting Trials (CONSORT) flow-chart of patient flow into the study; baseline characteristics of these patients were presented to compare the characteristics of excluded patients, eligible patients who declined participation, and patients included in the study. For participants who received their allocated intervention, baseline characteristics were presented according to their treatment allocation.

Recruitment rate was calculated by capturing the number of new participants entering the study each calendar month and presenting a cumulative total across the recruitment period. Retention rate was calculated through determining the number of participants who completed the full period of IMP. An AE log was maintained through the study; the number of AEs occurring in each arm was then determined at the end of the study and presented by severity and category group. A calculation of the number of unfilled assessments was performed as a percentage of the total number of assessments made; any questionnaire which featured a missing data point was marked as unfilled, thereby giving the most conservative estimate of assessment completion. At the end of the study, the participant and the assessor indicated which allocation group they believed the participant had been assigned; accuracy of this was calculated as a percentage of the total number of participants that correctly guessed their allocation.

Safety data was summarised by frequency of system affected using CTCAE v4.0 definitions. The total number of individual AEs, including severity grade, were also reported.

Post-trial review of participant perception was assessed using exit questionnaires and focus groups after study completion. The exit questionnaire is included in

appendix 5; the total number of participants who would wish to continue the IMP (if given the option), and who found the study beneficial, was calculated as a percentage of the total number of participants. A series of qualitative assessments of participant perception was undertaken using three moderated and audio-recorded focus groups; the full methods for this aspect of the study, and the results, are discussed in chapter 6.

Medication adherence

Adherence to study treatment was measured in the form of returned tablet counts, which was monitored as part of drug accountability at each visit. The number of capsules remaining was counted at each visit, as well as a calculation of the number of capsules expected to remain (for example, a participant receiving two capsules twice daily and seen exactly 14 days after the previous study visit, having been dispensed 56 capsules at that visit, would be expected to have zero capsules remaining). Adherence was determined at each visit. To account for potential expected remaining capsules (for participants who were seen early in their potential visit window), the difference between number of returned capsules and expected remaining capsules was calculated first. This value was used to determine adherence to the prescribed treatment. The formula for this is described below:

$$Adherence\ (\%) = 1 - \left(\frac{No.returned\ capsules - Expected\ remaining\ capsules}{Total\ number\ of\ capsules\ dispensed}\right) x100$$

As well as calculating the adherence to study medications as a percentage of doses taken, the number of participants considered adherent to their medication was calculated by determining the number of participants meeting 80% adherence, the threshold for sufficient adherence to treatment (283).

In addition, ECGs and observations (blood pressure and pulse) taken through the trial were reviewed post trial to observe any changes which may give an indication of adherence.

Secondary outcomes (clinical efficacy)

Estimation of clinical effect size was evaluated using the mean difference in fatigue scores (FAS and FACIT-Fatigue). In addition, mean differences in change of KSQ health status, anxiety and depression scores (HADS-A and HADS-D), health utility scores from EQ5D and SF36, patient reported health status from EQ-VAS, and sleep quality and efficiency (PSQI) were estimated. Analysis was performed using an intention-to-treat approach. For each measurement, the baseline score was measured during the baseline study visit (week 0); the only exception is the FAS score, which used the average value of their screening and baseline scores as this was felt more likely to reflect each participant's average fatigue score over time.

Activity data from the GENEActiv devices were analysed in two ways. Firstly, the raw data were analysed using the software GGIR within R-studio to determine the wear time and the amount of time spent in moderate or vigorous activity (MVPA). This was determined from previous work establishing the threshold values for MVPA using the GENEActiv device, identified as an ENMO value of 93.2milli-g determined from the device's accelerometer (257). Values for were determined for total time spent above this threshold for MVPA, as well as values adjusted for World Health Organization recommendations on "bouts" of MVPA time; this was defined in this study as at least 80% of any ten-minute period with activity intensity above the threshold for moderate activity (284). Moderate and vigorous activity thresholds for the activity monitor data were determined from previous work (257). Secondly, the raw data were converted to 15-second epoch data in comma separated value format by GENEActiv software (Activinsights, UK) and entered into a custom spreadsheet ("Sedentary Sphere"; A Rowlands (242, 243)) which calculated the number of minutes per day spent in sedentary behaviours based

upon posture classification and accelerometer output to determine when low-intensity activity in a sitting, reclined or lying position was likely to be occurring.

Only "valid" data, defined as a wear period more than ten hours per day for at least four of the seven days as used in previous studies (285), was used in analysis. The number of participants who wore the device for 24-hour periods on four or more days of the wear period was also recorded.

Statistical analysis

Participant flow

A two-stage CONSORT flow diagram was constructed to display the flow of patients through screening, enrolment and allocation. The first stage described the participant screening including the number of participants excluded, including reasons for exclusion or reasons for declining participation among patients who were otherwise eligible. The second stage described the enrolment, allocation and progression through the study, including patient withdrawal.

Outcomes and statistical analysis

An exploratory analysis of the clinical data captured during the study was undertaken on an intention to treat (ITT) basis, including all participants who received trial medication. Plots were constructed for each outcome, displaying the mean scores by allocation group at each visit and the change over time. Mean differences between allocation group were compared initially at each 6-week time point using a two-sample t-test (unadjusted analysis), with further analysis of the data using a general linear regression model to adjust the between-group mean difference for baseline values of the analysed outcome and level of baseline fatigue, the latter factor to balance for stratification of fatigue severity at baseline. In the case of the fatigue outcomes (FAS and FACIT-Fatigue instruments) which both have defined MCIDs, the number and proportion of participants meeting the MCID at each 6-week time point, compared with baseline values, was calculated. Data

analysis was undertaken using Stata statistical software version 14 (StataCorp, Texas, USA).

Substantial amendment

After four months of recruitment it became apparent that the recruitment rate was below that expected. In order to increase the recruitment period, two amendments were made. Firstly, the ability to recruit participants from PIC sites in the eastern region was added, with Royal Papworth Hospital and Addenbrooke's hospital operating in this capacity. Secondly, in order to increase the recruitment phase (and maximise the time participants could enter the study without reducing the overall study duration), follow-up for participants recruited between December 2017 and March 2018 was truncated. Participants randomised between 01/12/2017 and 01/02/2018 received study medication for 18 weeks, plus an additional two weeks if a down-titration period at the end of the study was required; participants randomised between 02/02/2018 and 02/03/2018 received study medication for 12 weeks, plus an additional two weeks if down-titration was required. The last date of follow-up was fixed at 06/07/2018.

As part of this substantial amendment, two additional outcome measures were added. The PSQI and Exit questionnaires were administered to patients entering the study after 23/05/2017 according to the questionnaire schedule in table 1; participants who had already commenced the study were administered the additional questionnaires if they consented to completing these additional measurements.

Trial approvals

The *FaST-MP* trial was registered with the clinicaltrials.gov database (registration number NCT02643732) on 31/12/2015. Research Ethics Committee (REC) approval was first gained on 21/06/2016 (East of England Cambridge Central Research Ethics Committee, REC reference 16/EE/0087). MHRA approval (EudraCT number 2016-

000342-60) was initially gained on 26/08/2016. The study was registered with the NIHR clinical research network portfolio (central portfolio management system ID 32754).

The substantial amendment described earlier was approved by REC on 21/04/2017, also requiring Health Research Authority (HRA) approval at that time due to changes in the REC and local site-specific approval since the initial application. HRA approval was gained on 21/04/2017, with MHRA approval for the amendment on 23/05/2017.

4.3 Conclusions

In this chapter, the methods for the *FaST-MP* study are described; these methods were published (286) after study opening to ensure greater transparency of the research process, helping identify where changes may have been made during the undertaking of the study and reduce bias in reporting outcomes. In the next chapter, the outcomes from the study are reported and discussed.

Chapter 5: *Fatigue and Sarcoidosis – Treatment with Methylphenidate (FaST-MP) feasibility study results*

Clinical Trial Registry – Registered with clinicaltrials.gov
Registry number - NCT02643732

Research Ethics Committee (REC) Approval Gained
REC reference – 16/EE/0087

Medicines and Healthcare Products Regulatory Agency Clinical Trial Authorisation
EudraCT Number – 2016-000342-60

5.1 Introduction

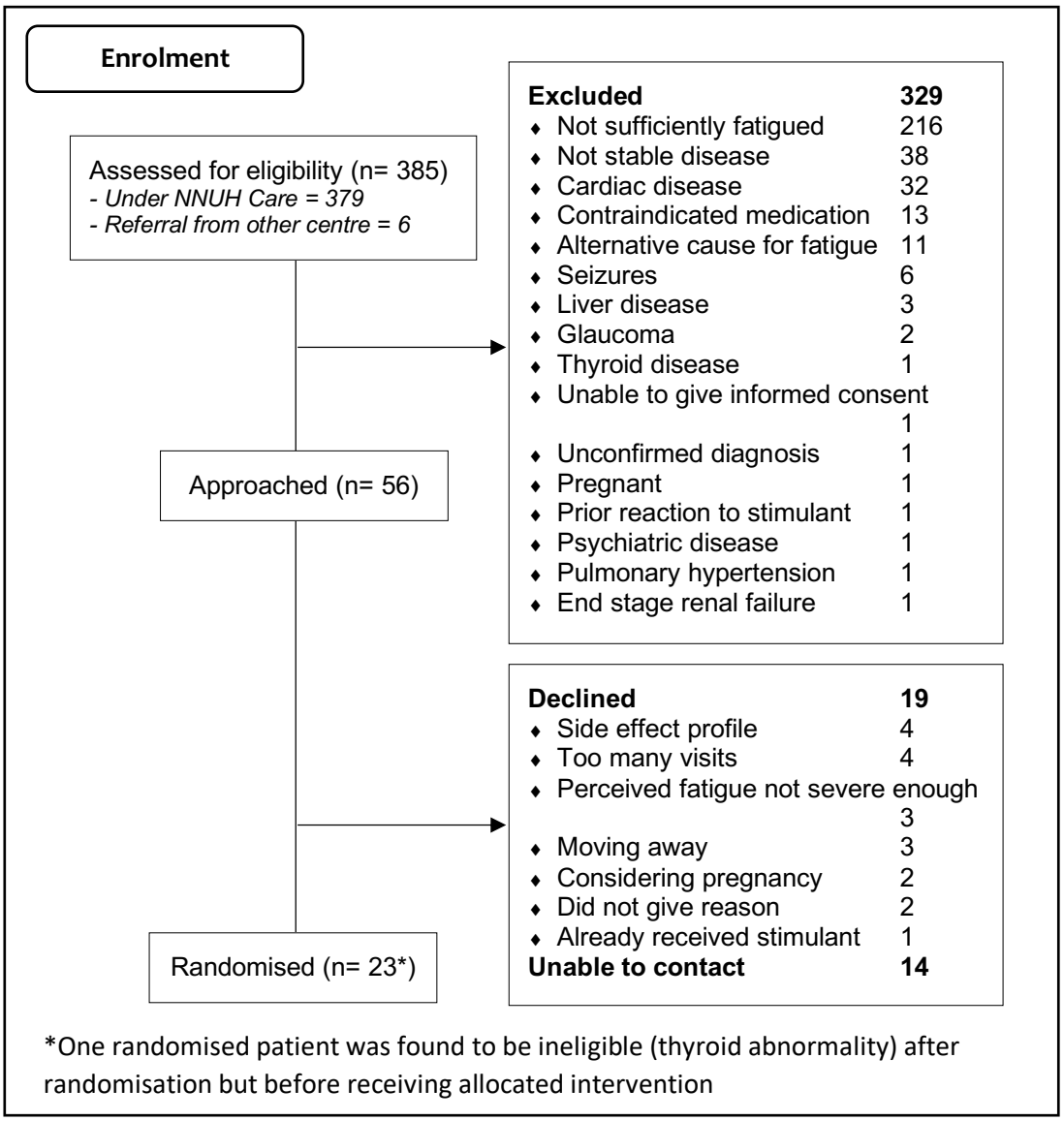
The previous chapter described the methods for the *FaST-MP* study, including the substantial amendment which was submitted after the study opened. In this chapter, the results of the quantitative data collected within the study are described in detail, including for the primary outcomes surrounding the feasibility of an appropriately-sized phase III study investigating the clinical efficacy of methylphenidate for sarcoidosis-associated fatigue, the safety data recorded, and the exploratory clinical outcomes recorded in both the methylphenidate and placebo arms.

5.2 Results

Screening and enrolment

A total of 385 patients with sarcoidosis were evaluated against the inclusion and exclusion criteria between 07/11/2016 and 02/03/2018. Of these, 329 were excluded prior to being approached. The remaining 56 patients were approached about participating in the study, of which 23 were included in the study and underwent randomisation – one randomised participant was randomised in error after being found to be ineligible due to breaching an exclusion criteria (hyperthyroidism) between randomisation and receiving their allocated intervention. The number of people who were excluded or declined to participate in the study, including reasons why, are shown in the CONSORT flow chart (Figure 7).

***Figure 7** - CONSORT flow-chart part 1: participant enrolment*



Of the 385 participants assessed for eligibility, six were referred from other centres and did not receive their usual care at the NNUH. In total, 379 patients were identified as having sarcoidosis and receiving follow-up by the respiratory medicine department at the NNUH.

Within the 379 NNUH patients assessed, 169 (44.6%) had reported fatigue or related symptoms (tiredness, lack of energy) during previous clinical visits. The most common cause for exclusion amongst patients reporting fatigue was active disease requiring ongoing changes to treatment ("Not stable disease"), with cardiac disease being the most common alternative medical condition preventing inclusion

in the study (n = 32). Of the six patients referred from other centres, two were excluded from the study before randomisation; one had glaucoma and one had a history of seizures. A total of 52 eligible patients were identified from the NNUH patient population, representing 13.7% of the hospital's population with pulmonary sarcoidosis. Of these 52 eligible patients from the NNUH sarcoidosis cohort, 33 patients (63.5%) declined to take part or were unable to be contacted by the study team and 19 (36.5%) consented to participate. In total, only 5.0% of the NNUH sarcoidosis cohort were eligible and willing to participate.

Over the 16 months that the study was open to recruitment, the average monthly recruitment rate was 1.4 participants per month (including recruitment from outside the NNUH), or 1.2 participants per month from the NNUH population alone.

Comparison of characteristics between patient groups

To determine if the participants included in the study were significantly different from other patients with sarcoidosis, clinical characteristics of these patients were compared with the clinical data of those who were not included in the study. All patients who were assessed for inclusion in the study were split into three groups; those who were not fatigued or did not describe fatigue as a significant problem (group 1), those who reported fatigue as a clinical problem but who met one or more of the exclusion criteria for the study (group 2), and those who reported fatigue as a problem but declined to participate in the study (group 3). The clinical characteristics for each group are shown in Table 18. No statistical tests were applied between groups; apparent differences between groups considered potentially significant are highlighted in bold.

Table 18 - Characteristics of non-fatigued, fatigued but ineligible, fatigued but declined participation and eligible randomised participants

	Group 1 – Non-fatigued	**Group 2 – Fatigued, Ineligible**	**Group 3 – Fatigued, Eligible, Declined**	**Group 4 – Fatigued, Eligible, Randomised**
Number (% total cohort)	216 (56.1)	114 (29.6)	33 (8.6)	22 (5.7)*
Age	56.8 (14.6)	54.9 (13.5)	**49.3 (12.5)**	56.0 (9.2)
Female sex (%)	91 (42.1)	50 (43.8)	**20 (60.6)**	9 (40.9)
Caucasian (%)	210 (97.7)	113 (99.1)	30 (90.9)	22 (100)
BMI	32.8 (8.1)	32.6 (7.9)	30.4 (7.7)	31.5 (5.8)
FEV1 (% predicted)	91.5 (23.0)	**84.2 (22.7)**	92.6 (14.7)	92.7 (23.7)
FVC (% predicted)	99.8 (20.6)	**91.5 (21.0)**	98.1 (16.2)	100.0 (21.9)
DLCO (% predicted)	77.9 (22.4)	72.7 (19.3)	84.1 (9.3)	74.1 (20.0)
KCO (% predicted)	90.6 (23.7)	90.3 (18.8)	97.5 (12.8)	101 (11.3)
Disease duration (years)	9.1 (8.8)	7.4 (9.6)	**4.7 (4.6)**	7.8 (7.1)
Pulmonary disease (%)	212 (98.1)	113 (99.1)	32 (100)	22 (100)
Extrapulmonary disease	65 (30.1)	47 (41.2)	9 (27.3)	9 (40.9)
Initial CXR stage 0/1/2/3/4 (%)	22/85/38/45/10 (11/42.5/19/22.5/5)	15/42/20/24/5 (14.2/39.6/18.9/22.6/4.7)	3/16/5/5/0 (10.3/55.2/17.2/17.2/0)	4/10/2/1/1 (22.2/55.6/11.1/5.6/5.6)
sACE (presentation)	67.6 (42.0)	**84.7 (66.4)**	61.4 (28.7)	50.4 (27.6)
sACE (latest)	55.2 (31.2)	58.7 (40.8)	52.4 (20.1)	42.5 (19.3)
Calcium (presentation)	2.43 (0.19)	**2.49 (0.29)**	2.45 (0.15)	2.43 (0.10)
Calcium (latest)	2.41 (0.10)	2.42 (0.10)	2.39 (0.08)	2.43 (0.09)
Receiving steroids (%)	44 (20.4)	**63 (55.2)**	**3 (9.1)**	5 (22.7)
- **Mean dose (mg)**	- 7.4 (4.3)	- **15.4 (9.1)**	- **15.7 (12.5)**	- 10.3 (6.9)
Receiving other immunosuppressant (%)	**15 (6.9)**	19 (16.7)	5 (15.2)	3 (13.6)

Abbreviations: BMI – Body Mass Index; FEV1 – Forced Expiratory Volume in 1 second; FVC – Forced Vital Capacity; DLCO – Diffusing capacity of the lungs for carbon monoxide (single-breath hold); KCO – Transfer co-efficient of carbon monoxide; CXR – Chest X-Ray; sACE – Serum Angiotensin Converting Enzyme

*23 participants were randomised but one participant was discovered to be ineligible prior to receiving the intervention; their details are included in Group 2.

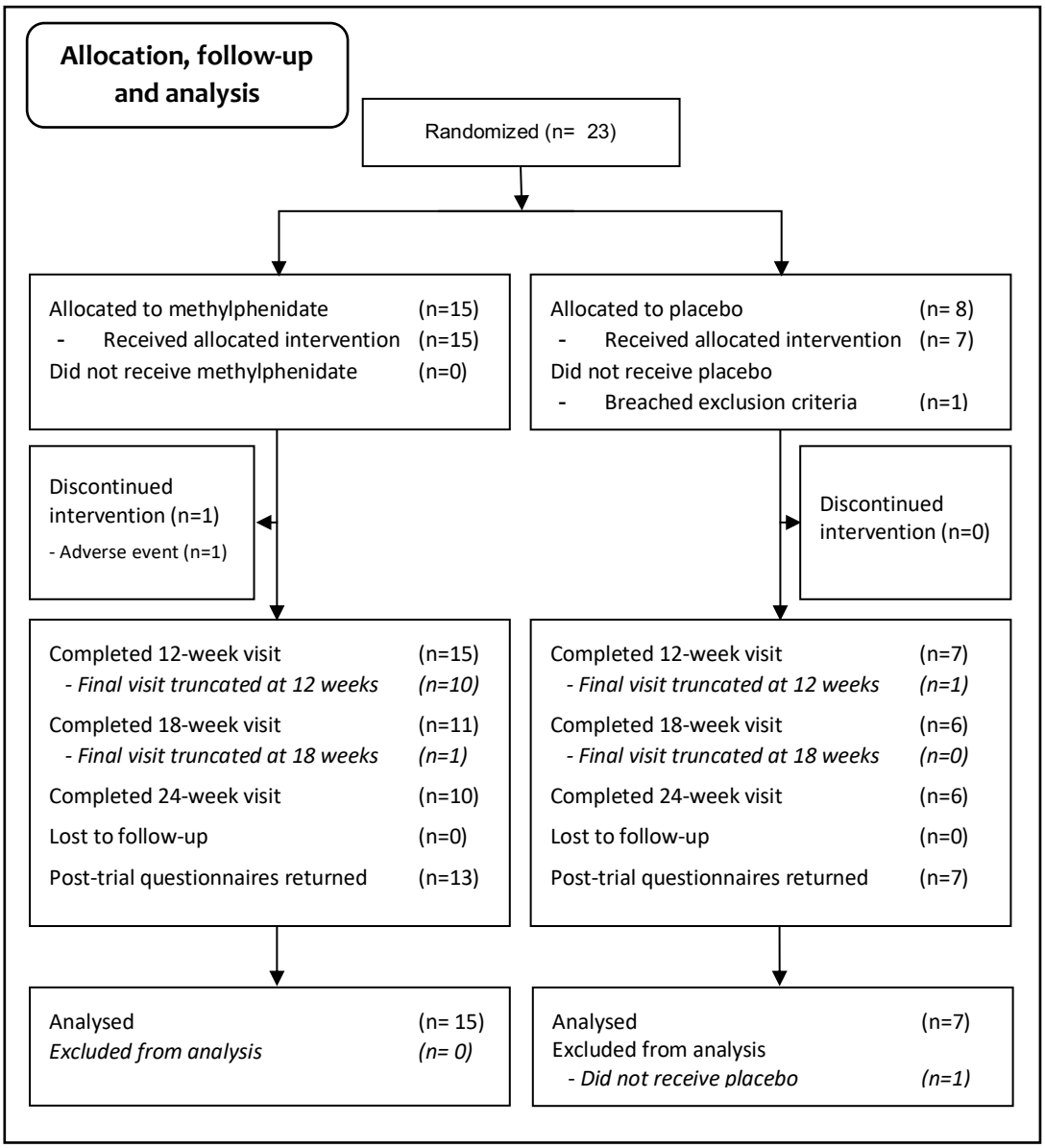
Participant recruitment and retention

Of the 23 participants recruited to the study, 19 were recruited from patients under the care of the NNUH, equating to 5.0% of the sarcoidosis patient population at the NNUH. Four participants recruited from other centres were randomised, although one patient was found to be ineligible after randomisation and did not receive the allocated intervention (placebo); this patient was not included in the analysis. The study was open for recruitment between the 7th November 2016 and 2nd March 2018, a total of 16 months. Recruitment across the period varied significantly; the highest recruitment for a single month was five participants, which occurred in March 2017 and February 2018. The mean recruitment rate was 1.4 participants per month, ranging between 0 and 5 participants per month.

Of the 23 participants randomised within the study, one was excluded after randomisation due to the patient being randomised in error (found to have hyperthyroidism requiring treatment after randomisation but prior to receiving study medications). The remaining 22 participants received their allocated intervention, and all completed their planned study visits. Due to the previously described substantial amendment, not all participants completed the same duration of follow-up. Participants 1-16 completed the full 24-week follow-up period, covering eight study visits, as well as returning data six-weeks after study completion. Participant 17 completed 18-weeks follow up (seven study visits plus post-trial questionnaires) and the remaining participants completed 12-weeks follow-up (six visits plus post-trial questionnaires). The flow-chart for participant progress through the study is shown in Figure 8.

All patients who received their allocated intervention completed all scheduled visits. One participant discontinued trial medications due to cardiac-type chest pain at week 20 but completed their planned visits.

***Figure 8** - CONSORT flow chart part 2: allocation, follow-up and analysis*



Baseline characteristics

The baseline characteristics of the participants who received their allocated intervention in the study are shown in Table 19. Baseline characteristics were well balanced between groups, although a greater proportion of females were seen in the placebo group (57.1% vs 33.3% in the methylphenidate arm). A greater proportion of the placebo group were also receiving treatment for their disease at the time of randomisation (57.2% vs 26.7%). The baseline scores for each outcome measure are shown in Table 20. In keeping with the number of participants in the

placebo group receiving immunosuppression, pulmonary function was worse in the placebo group than in the methylphenidate group; this was reflected in a lower lung-related disease-specific health status (KSQ-Lung) score (58.8 vs 43.7). Baseline physical activity levels varied significantly within groups but were lower (by total time in MVPA) in the placebo group than the methylphenidate group (87.4 minutes/day vs 105.7 minutes/day).

***Table 19** - Baseline characteristics by group*

Variable	Methylphenidate (n = 15)	Placebo (n=7)
Age at randomisation (years)	55.5 (10.1)	55.4 (7.7)
Gender (%)		
Male	10 (66.7)	3 (42.9)
Female	5 (33.3)	4 (57.1)
Smoking status (%)		
Current	0 (0.0)	0 (0.0)
Ex	4 (26.7)	3 (42.9)
Never	11 (73.3)	4 (57.1)
Smoking history (pack years)	17.5 (14.2)	6.7 (4.9)
Alcohol intake (units/week)	5.3 (7.6)	4.7 (10.3)
Body Mass Index (kg/m^2)	30.3 (4.5)	33.8 (7.6)
Weight (kg)	94.0 (16.8)	94.0 (21.3)
Blood pressure, systolic (mmHg)	145.4 (16.3)	135.6 (24.7)
Blood pressure, diastolic (mmHg)	88.7 (10.7)	85.9 (9.7)
Pulse (beats per minute)	73.5 (16.4)	75.9 (9.8)
Disease duration at randomisation (years)	6.7 (7.1)	6.0 (7.8)
>3 years	*9 (60.0)*	*4 (57.1)*
1-3 years	*2 (13.3)*	*2 (28.6)*
<1 year	*4 (26.7)*	*1 (14.3)*
Pulmonary disease (%)	15 (100.0)	7 (100.0)
Extrapulmonary disease (%)	9 (60.0)	3 (42.9)
Ethnicity		
Caucasian	15 (100.0)	7 (100.0)
Current treatment for sarcoidosis	4 (26.7)	4 (57.2)
Prednisolone	3 (20.0)	1 (14.3)
Methotrexate	1 (6.7)	2 (28.6)
Azathioprine	0 (0.0)	1 (14.3)

Values presented as means (standard deviations) or frequencies (%)

Abbreviations: kg – kilograms; m – metres; mmHg – millimetres of mercury

***Table 20** - Baseline scores in each outcome measure by group*

Outcome (baseline score)	Methylphenidate	Placebo
FAS score[1]	35.9 (7.7)	35.9 (8.8)
FAS score 22-34 (%)	7 (46.7)	3 (42.9)
FAS score 35-50 (%)	8 (53.3)	4 (57.1)
FACIT-Fatigue score[1]	19.9 (11.0)	20.0 (10.8)
HADS-A[2]	7.8 (3.3)	8.0 (4.9)
HADS-D[2]	7.9 (2.9)	6.6 (4.5)
EQ5D Utility[3]	0.694 (0.271)	0.679 (0.244)
EQ-VAS (mm)[3]	62.5 (21.9)	68.0 (12.9)
SF-6D Utility[3]	0.613 (0.094)	0.559 (0.164)
KSQ General Health Status[4]	48.8 (12.8)	47.1 (11.8)
KSQ Lung[4]	58.8(16.5)	43.7 (15.8)
KSQ Medications[4]	86.0 (20.3)	85.6 (23.2)
KSQ Skin[4]	86.0 (21.4)	87.5 (17.3)
KSQ Eyes[4]	66.7 (21.5)	62.6 (22.5)
KSQ Composite[4]	54.2 (7.7)	50.0 (6.7)
PSQI Score[5]	8.9 (4.1)	13.5 (3.4)
Sleep efficiency (% of night asleep)	86.9 (27.7)	55.4 (15.9)
FEV1 (percentage of predicted value)	99.5 (24.1)	79.1 (19.0)
FVC (percentage of predicted value)	104.3 (21.7)	88.6 (18.4)
MSWT (m)	522.7 (330.9)	438.6 (353.6)
Sedentary time (minutes/day)	644.4 (152.8)	602.5 (118.7)
MVPA (minutes/day)	105.7 (68.3)	87.4 (43.9)
$MVPA_{10}$ (minutes/day)[6]	19.0 (25.4)	4.6 (5.0)

Values presented as means (standard deviations) or frequencies (%)

Abbreviations: FAS – Fatigue Assessment Scale; FACIT – Functional Assessment of Chronic illness therapy; EQ5D – EuroQoL 5 Dimension, 5 level; EQ-VAS – EuroQoL Visual Analogue Scale; SF6D – Short form 6 dimension; KSQ – Kings Sarcoidosis Questionnaire; PSQI – Pittsburgh Sleep Quality Index; FEV1 – Forced Expiratory Volume in 1 second; FVC – Forced Vital Capacity; MSWT – Modified Shuttle Walk Test; MVPA – Moderate or Vigorous Physical Activity

[1]Fatigue score values; Higher FAS scores indicate greater levels of fatigue, lower FACIT-Fatigue scores indicated greater levels of fatigue

[2]Depression and anxiety scores; Higher scores indicate greater level of anxiety or depression symptoms

[3]Health utility scores; Higher values indicate greater health utility (greater quality of life)

[4]Disease specific quality of life; Lower values indicate greater problems with health related to sarcoidosis. Each subscale relates to an organ system potentially affected by sarcoidosis, the composite value considers all organ systems and general health status.

[5]PSQI score indicates overall quality of sleep – lower values indicate better quality.

[6]$MVPA_{10}$ = Activity only counted if >80% of any 10 minute period above threshold for MVPA

Medication adherence

Adherence to study medications was excellent throughout the study. Median adherence to prescribed medications across each group was never lower than 96%. Levels of adherence were similar between groups (Table 21), with all but one participant meeting at least 80% adherence with prescribed medications; this participant was included in the analysis. No changes in adherence levels were seen over the duration of the study to suggest adherence reduced at any point during the study.

Table 21 - Adherence rates to study medication (% adherence) by allocation group for period (weeks) and overall adherence

	Methylphenidate			Placebo		
Week	**n**	**Median % (IQR)**	**≥80%**	**n**	**Median % (IQR)**	**≥80%**
0-2	15	100 (95-100)	13 (87)	7	100 (100-100)	7 (100)
2-4	15	100 (96-100)	15 (100)	7	100 (99-100)	7 (100)
4-6	15	98 (93-100)	14 (93)	7	100 (97-100)	7 (100)
6-12	15	99 (96-100)	13 (87)	7	100 (99-100)	6 (86)
12-18	11	100 (98-100)	10 (91)	6	100 (99-100)	5 (83)
18-24	10	96 (89-100)	8 (80)	6	97 (91-100)	6 (100)
Overall	15	98 (90-100)	15 (100)	7	99 (97-100)	6 (86)

Data completeness

Data completeness was excellent throughout, with no single instrument having greater than 5% missing data. The missing data rate across all data points was only 2.6%, indicating that participants could reliably complete the questionnaires despite many instruments being administered simultaneously at most study visits. The completion rate for other measures was also good, although there was a problem with loss of facilities to safely undertake the MSWT towards the end of the study; for this reason, six MSWT (10% of the total data points) were not undertaken. Only one other MSWT was not undertaken; this was due to a participant feeling unable to undertake the test due on the day. Only three data points were missing for the activity monitors; two missing data points were due to

the devices not being worn (zero data on device), the other was a non-returned device which was lost in the process of being returned. The full range of missing data points for the clinical outcomes are shown in Table 22.

***Table 22** - Completion rates for questionnaires and other outcomes performed during the study, including missing data rate*

Outcome	Expected data points - n	Missing Data points - n (%)
FAS	165	2 (1.2)
FACIT-Fatigue	165	2 (1.2)
HADS	121	4 (3.3)
KSQ	121	3 (2.5)
EQ5D	121	3 (2.5)
SF36	121	4 (3.3)
Costs (Health economics)	60	2 (3.3)
Safety[1]	104	5 (4.8)
PSQI[2]	43	2 (4.7)
Spirometry (FEV1 and FVC)[3]	60	3 (5.0)
MSWT[4]	60	7 (11.7)
Activity monitor data[5]	60	3 (5.0)
Total	1142	30 (2.6)

Acronyms: FAS – Fatigue Assessment Scale; FACIT-Fatigue – Functional Assessment of Chronic Illness Therapy – Fatigue; HADS – Hospital Anxiety and Depression Scale; KSQ – Kings Sarcoidosis Questionnaire; EQ5D – EuroQoL 5 Dimension 5 Level scale; SF36 – Short Form 36; PSQI – Pittsburgh Sleep Quality Index; FEV1 – Forced Expiratory Volume in 1 second; MSWT – Modified shuttle walk test

[1]Safety questionnaire was administered up to week 12; participants completing a truncated time period who completed study medications at week 12 did not all receive safety questionnaires at their final visit (4 out of 5 missing data points).

[2]PSQI only administered following major amendment approved in April 2017; expected data points refers to the number of visits where the questionnaire should have been administered after the study amendment was approved.

[3]All missing spirometry values occurred in a single participant who was unable to perform the test without suffering syncope; spirometry was not performed for this participant

[4]Six of the seven missing MSWT values occurred due to loss of facilities to undertake the test

[5]Missing data points for activity watches refers to an unreturned device (1 missing data point) or device not worn during wear period (2 missing data points).

Medication safety and tolerability

Medication down-titration and discontinuations

Three participants (13.6%) required down-titration of their study medications and one participant (4.5%) required discontinuation of study medications. The three participants that required dose reduction decreased from 20mg (2 capsules) twice daily to 10mg (1 capsule) twice daily for reasons of significant anxiety (participant 3, week 6), increased and severe fatigue (participant 13, week 6) and dry mouth causing significant discomfort (participant 19, week 10). The participant who discontinued study medications suffered cardiac-type chest pain at week 22; this participant had previously reduced to 10mg twice daily due to significantly increased fatigue on the higher dose. Subsequent investigations did not identify a cardiac event as a cause for the pain, but the participant did not re-start medications. In addition, three participants did not increase their dose from 10mg to 20mg twice daily due to personal choice; in each case they felt that they had a good response to medications and did not wish to increase the dose further.

All dose reductions and withdrawals occurred in the methylphenidate group; all seven participants in the placebo group tolerated 2 capsules twice daily through the entire study and no patients required discontinuation of medications.

Adverse events

Across the 22 participants, 96 adverse events were observed including one serious adverse event. All but one participant developed an AE during the course of the study; the only participant who did not suffer an AE was allocated methylphenidate and was adherent to the medication throughout the study. The commonest systems affected were the nervous system, respiratory system and gastrointestinal system. The number of participants developing at least one AE in each organ system is shown in Table 23; the total number of adverse events stratified by organ system and severity is shown in table 24.

No cardiac events occurred during the study and no participants developed ECG abnormalities during the trial.

One SAE occurred during the study. This was an episode of syncope which appeared unrelated to the study medications; the participant was investigated for possible cardiac problems or arrhythmia but none were found and the participant was able to continue the study medications to the end of the study.

Table 23 *- Adverse event rates by treatment allocation; number of participants in each arm developing at least one AE within each individual organ system*

CTCAE System Class	**Methylphenidate** Number of participants with ≥1 event (%)	**Placebo** Number of participants with ≥1 event (%)
Ear and labyrinth	2 (13.3)	0
Eye	1 (6.7)	3 (42.9)
Gastrointestinal	7 (46.7)	1 (14.3)
General disorders	2 (13.3)	2 (28.6)
Infections and infestations	1 (6.7)	1 (14.3)
Investigations	2(13.3)	0
Metabolism and nutrition	1 (6.7)	0
Musculoskeletal	5 (33.3)	1 (14.3)
Nervous system	10 (66.7)	3 (42.9)
Psychiatric	5 (33.3)	3 (42.9)
Respiratory	7 (46.7)	6 (85.7)
Reproductive system and breast	1 (6.7)	0
Skin and subcutaneous tissue	4 (26.7)	1 (14.3)
Vascular disorders	2 (13.3)	0
Any	14 (93.3)	7 (100.0)

Abbreviations: CTCAE – Common Terminology Criteria for Adverse Events

Table 24 *- Total number of adverse events occurring (including percentage of total within each treatment allocation) by organ system*

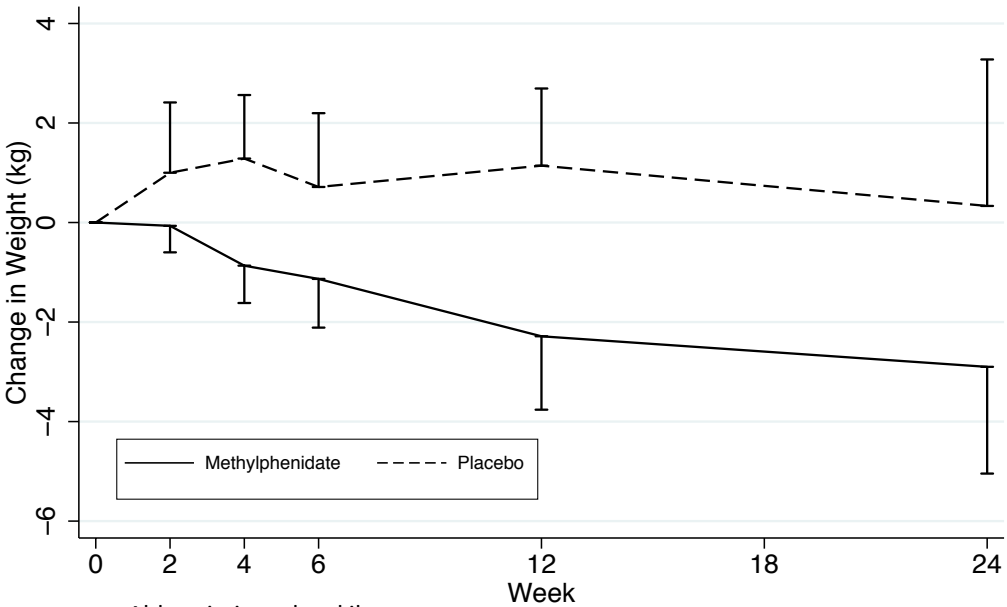
	Methylphenidate (n=15)					Placebo (n=7)				
CTCAE Organ Class	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Ear and labyrinth	2 (2.7)	0	0	0	0	0	0	0	0	0
Eye	1 (1.4)	0	0	0	0	3 (13.0)	0	0	0	0
Gastrointestinal	13 (17.8)	2 (2.7)	0	0	0	1 (4.3)	0	0	0	0
General disorders	2 (2.7)	2 (2.7)	0	0	0	1 (4.3)	1 (4.3)	0	0	0
Infections and infestations	1 (1.4)	0	0	0	0	0	1 (4.3)	0	0	0
Investigations	2 (2.7)	0	0	0	0	0	0	0	0	0
Metabolism and nutrition	1 (1.4)	0	0	0	0	0	0	0	0	0
Musculoskeletal	3 (4.1)	2 (2.7)	0	0	0	0	1 (4.3)	0	0	0
Nervous system	14 (19.2)	1 (1.4)	1 (1.4)	0	0	3 (13.0)	0	0	0	0
Psychiatric	2 (2.7)	3 (4.1)	0	0	0	2 (8.7)	2 (8.7)	0	0	0
Respiratory	9 (12.3)	4 (5.5)	0	0	0	6 (26.1)	1 (4.3)	0	0	0
Reproductive system and breast	2 (2.7)	0	0	0	0	0	0	0	0	0
Skin and subcutaneous tissue	2 (2.7)	2 (2.7)	0	0	0	0	1 (4.3)	0	0	0
Vascular disorders	1 (1.4)	1 (1.4)	0	0	0	0	0	0	0	0
Any adverse event	55 (75.3)	17 (23.3)	1 (1.4)	0	0	16 (69.6)	7 (30.4)	0	0	0

Safety monitoring was undertaken throughout the study for all participants, consisting of measurements of blood pressure, pulse and weight at weeks 2, 4, 6, 12 and 24. Mean baseline systolic blood pressure was 10mmHg higher in the methylphenidate group than the placebo group (145.4mmHg vs 135.8mmHg) but there were no differences in mean diastolic blood pressure, pulse rate or weight at baseline between the two arms.

Figure 9 shows the change in recorded weight at each visit compared with baseline weight. No change was seen in the placebo arm compared with baseline (mean change 0.3kg increase) whereas the methylphenidate group saw a mean reduction in weight by 2.9kg. Weight loss is a known side effect of methylphenidate and this difference is an expected effect of the treatment.

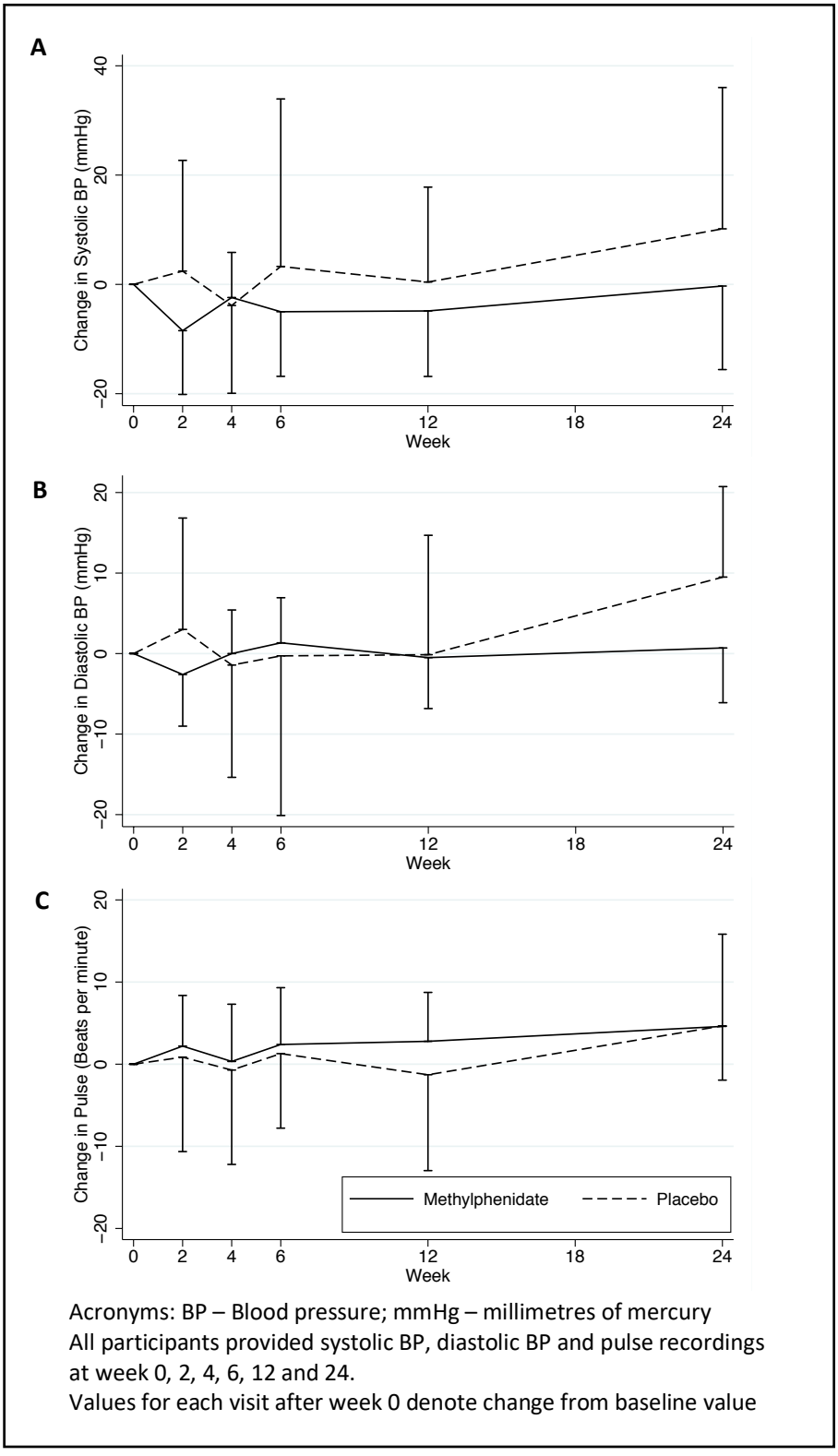
No differences were seen in changes in systolic blood pressure, diastolic blood pressure or resting pulse rate (Figure 10) over the duration of the study in either arm; data was unavailable at week 30 as this time-point consisted of questionnaires returned via post only.

Figure 9 *- Change in weight (kg) across the duration of the study, stratified by treatment arm. Results are mean values with 95% confidence intervals*



Abbreviations: kg - kilograms
All participants provided weight recordings at week 0, 2, 4, 6, 12 and 24.
Values for each visit after week 0 denote change from baseline value

Figure 10 *- Change in systolic BP (A), diastolic BP (B) and pulse rate (C) compared with baseline values across the duration of the study, stratified by treatment arm. Results are mean values with 95% confidence intervals*



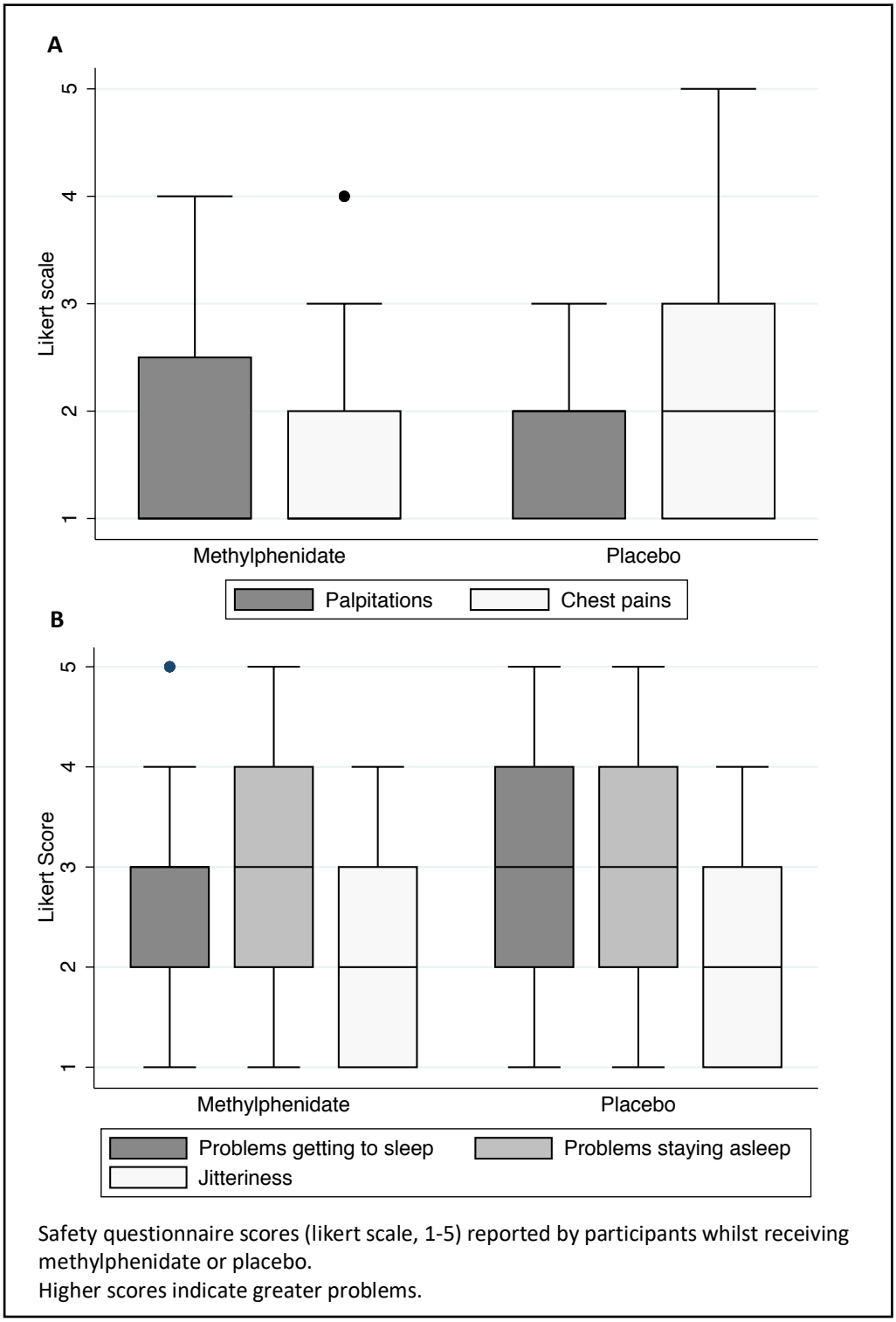
Acronyms: BP – Blood pressure; mmHg – millimetres of mercury
All participants provided systolic BP, diastolic BP and pulse recordings at week 0, 2, 4, 6, 12 and 24.
Values for each visit after week 0 denote change from baseline value

Participant-reported problems and side-effects were captured using five-point likert scales within a safety questionnaire. The results are shown are shown in Figure 11, displayed as median, interquartile range and total range of participant-reported values across the study, where participants were receiving medications.

No differences were seen between the two arms of the study, either in cardiac or non-cardiac symptoms. In keeping with the sleep quality and efficiency results, methylphenidate did not lead to increased problems with sleep onset or sleep maintenance compared with the placebo arm. The score for cardiac symptoms (palpitations and chest pains) was slightly higher in the placebo arm compared with the methylphenidate arm (median score 0 vs 1 for both palpitations and chest pain).

The results suggest that participants receiving methylphenidate did not develop symptomatic cardiac problems during the study. This is in keeping with the ECG data, with no participants developing new ECG abnormalities during the course of the study in either arm.

Figure 11 *- Box and whisker plots denoting reported problems in the safety questionnaire (likert scales) whilst receiving medications. Plots are split into cardiac-related symptoms (A) and non-cardiac symptoms (B). The central box represents the interquartile range*



Safety questionnaire scores (likert scale, 1-5) reported by participants whilst receiving methylphenidate or placebo.
Higher scores indicate greater problems.

Activity monitor use

There were 60 planned wear periods across the 22 participants who received study medications. The data regarding device return rates and data validity are shown in Table 25. Three data points (5.0% of all wear periods) were missing from the activity monitor data – two were due to the participant failing to wear the device at any point during the monitoring period and one was due to loss of device during the process of returning the monitor. The missing device was never recovered. Of the remaining data, two participants failed to wear the activity monitor for sufficient duration to calculate at one time period apiece; in total, five data points were missing to the extent that no activity data could be calculated for that period. Data validity was defined as any participant wearing the activity monitor for at least 10 hours across four days. Fifty-four wear periods recorded sufficient data to be considered valid (90.0% of the total wear periods, 98.2% of devices that returned any data). Of the participants who returned valid data, the majority had worn their device for full 24-hour periods; between 86.7% and 95% of participants returning minimum valid data had worn the device for at least four full 24-hour periods.

Table 25 *- Activity monitor data relating to device return rates and data validity*

Period	No. participants	Devices returned (%)	Any data returned (%)	Minimum valid data[1] (%)	Wear for 24h periods[2]
Week 0	22	22 (100.0)	20 (90.9)	20 (90.9)	19 *(95.0)*
Week 12	22	21 (95.5)	20 (90.9)	19 (86.4)	17 *(89.5)*
Week 24	16	16 (100.0)	15 (93.8)	15 (93.8)	13 *(86.7)*
Total	60	59 (98.3)	55 (91.7)	54 (90.0)	49 *(90.7)*

[1]Defined as at least 10 hours of wear time per 24 hours in at least two weekdays and two weekend days

[2]The number of participants returning minimum valid data who wore the device for 24-hour periods on at least four days of the wear period

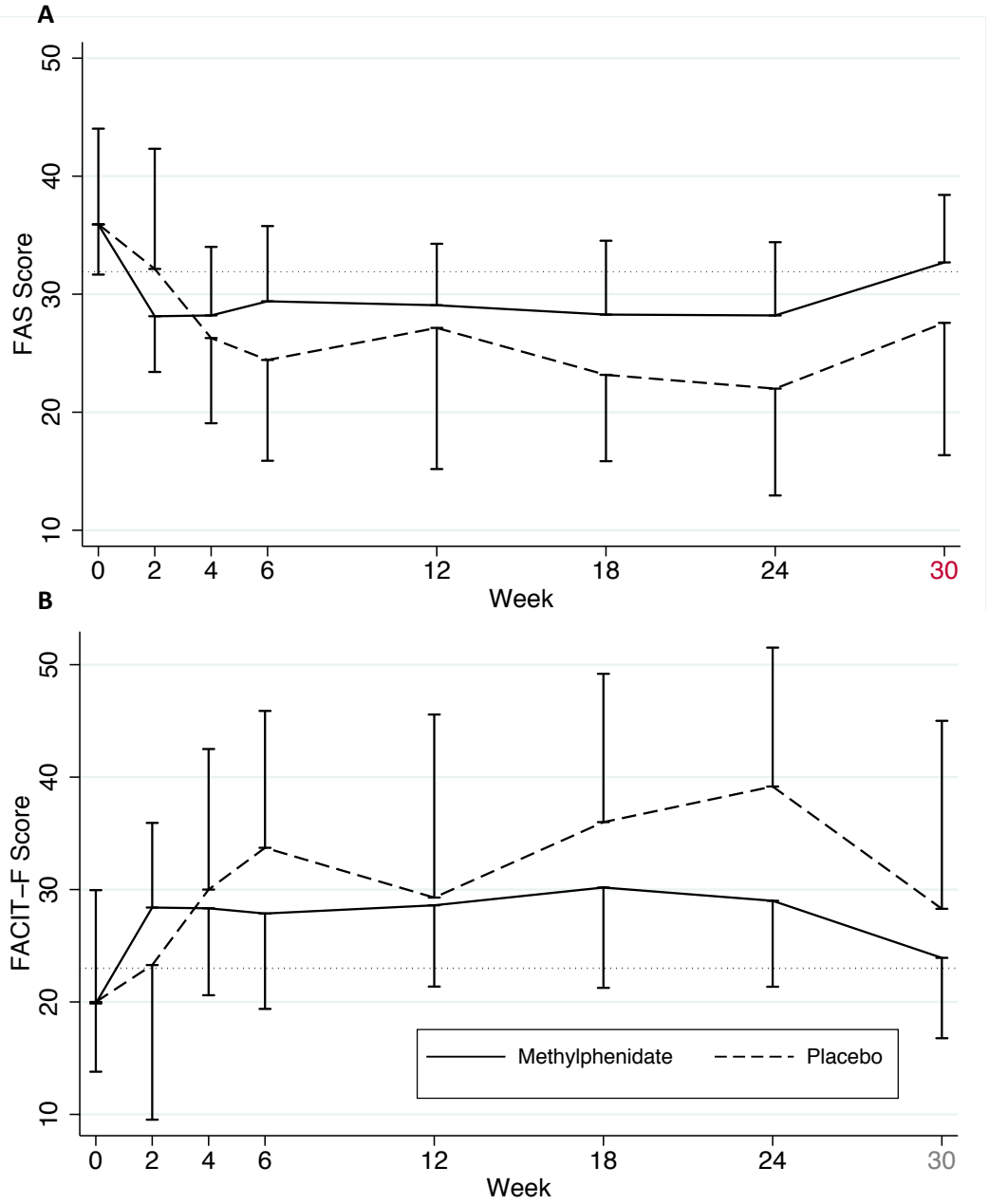
Secondary clinical outcomes

Fatigue

Baseline fatigue scores were well-balanced between arms. The baseline FAS score was 35.9 in both arms and the baseline FACIT-fatigue score was 19.9 in the methylphenidate arm and 20.0 in the placebo arm. Both groups showed a reduction in fatigue, scored by both the FAS and FACIT-Fatigue scores, although a greater mean improvement in both fatigue scores was seen in the placebo arm.

Figure 12 shows the changes in both FAS and FACIT-Fatigue scores from baseline values plotted over time and stratified by allocation group. The mean change at each time point is greater than the MCID for each questionnaire in both groups, although the extent of change in both fatigue scores is greater in the placebo arm than in the methylphenidate arm. The size of effect appears similar throughout all visits, suggesting that the effect seen from the medications in each arm was sustained. Both groups showed increases in fatigue levels at 6 weeks post-medication (week 30 time-point). The mean value for the placebo arm remained below the MCID for both questionnaires whereas the methylphenidate arm showed a return to near-baseline FAS scores, suggesting any effect seen whilst receiving the trial medication did not persist on discontinuing medications.

***Figure 12** - Change in fatigue scores (FAS (A) and FACIT-Fatigue (B) questionnaires) from baseline values over time, stratified by allocation. Results are mean values with 95% confidence intervals*



Number of participants per time-point:
Methylphenidate: Weeks 0-12 - 15; Week 18 – 11; Week 24 – 10
Placebo: Weeks 0-12 – 7; Week 18 – 6; Week 24 – 6
Week 30 time-point includes all data for participants returning data six-weeks after completing medications (n=13 for methylphenidate arm, n=7 for placebo arm)
Horizontal dotted line = Minimal clinically important difference for the questionnaire
FAS – Higher scores = worse fatigue; FACIT-Fatigue – Lower scores = worse fatigue

Tables 26 and 27 show the mean scores during study follow-up and the between-group differences for the FAS and FACIT-Fatigue questionnaires respectively, both unadjusted and adjusted for baseline fatigue severity. The results of the unadjusted between-group analysis showed that the FAS score was lower in the placebo arm, 1.92 to 6.20 points less than the methylphenidate arm, consistent with lower levels of fatigue in the placebo group. The FACIT-Fatigue scores showed a similar trend; participants in the placebo arm had a higher FACIT-Fatigue score, consistent with lower fatigue levels, compared with those allocated methylphenidate (between 0.69 and 10.17 points higher in the placebo arm whilst receiving medications).

Adjustment of the between-group differences for baseline values of each outcome led to some modification of the results. Participants allocated to methylphenidate had a higher FAS score than those receiving placebo, on average, whilst receiving the medication, varying between 1.7 and 6.2 points greater, consistent with higher fatigue levels in the methylphenidate arm; at six-weeks after discontinuing medications the placebo arm had an adjusted mean FAS score 7 points lower than the methylphenidate group (95% CI 1.3, 12.8 points), consistent with significantly lower fatigue post-trial. The FACIT-Fatigue scores in the methylphenidate arm were between 0.4 and 9.2 points lower than the placebo arm, also consistent with higher fatigue levels in participants allocated methylphenidate; at 24 weeks the between-group difference was significant (9.2 points, 95% CI -17.8, -0.6 points).

***Table 26** - Fatigue scores measured by Fatigue Assessment Scale (FAS) questionnaire during follow-up, including between-group differences*

	Methylphenidate		Placebo		Unadjusted difference[1,2]		Adjusted difference[1,3]	
Week	**n**	**Mean (S.D.)**	**n**	**Mean (S.D.)**	**Mean**	**95% C.I.**	**Mean**	**95% C.I.**
0	15	35.9 (7.7)	7	35.9 (8.8)	0.0	-7.7, 7.6	-	-
6	15	29.4 (11.5)	7	24.4 (9.2)	5.0	-5.4, 15.4	4.6	-2.9, 12.0
12	15	29.1 (9.4)	7	27.1 (12.9)	1.9	-8.2, 12.0	1.7	-5.4, 8.7
18	11	28.3 (9.3)	6	23.2 (7.0)	5.1	-4.2, 14.4	4.5	-3.1, 12.0
24	10	28.2 (8.7)	6	22.0 (8.6)	6.2	-3.4, 15.8	6.2	-1.4, 13.7
30	13	32.7 (9.5)	7	27.6 (12.1)	5.1	-5.2, 15.4	7.0	1.3, 12.8

Higher values indicate greater reported fatigue symptoms.

[1]Mean difference is equivalent to the *methylphenidate group value* minus the *placebo group value*. Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

[2]Between-group difference tested using two-sample t-test with equal variance

[3]Between-group difference tested using linear regression analysis performed with adjustment for baseline fatigue severity and FAS score at visit 0

***Table 27** - Fatigue scores measured by Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-Fatigue) questionnaire during follow-up, including between-group differences*

	Methylphenidate		Placebo		Unadjusted difference[1,2]		Adjusted difference[1,3]	
Week	**n**	**Mean (S.D.)**	**n**	**Mean (S.D.)**	**Mean**	**95% C.I.**	**Mean**	**95% C.I.**
0	15	19.9 (11.0)	7	20 (10.8)	-0.1	-10.5, 10.3	-	-
6	15	27.9 (15.3)	7	33.7 (13.2)	-5.9	-19.9, 8.2	-5.5	-15.3, 4.2
12	15	28.6 (13.1)	7	29.3 (17.6)	-0.7	-14.6, 13.2	-0.4	-9.1, 8.2
18	11	30.2 (13.3)	6	36.0 (12.6)	-5.8	-19.9, 8.3	-4.5	-14.9, 5.9
24	10	29.0 (10.7)	6	39.2 (11.8)	-10.2	-22.5, 2.1	-9.2	-17.8, -0.6
30	13	23.9 (11.8)	7	28.3 (18.1)	-4.4	-18.8, 9.6	-6.9	-14.7, 1.0

Lower values indicate greater reported fatigue symptoms.

[1]Mean difference is equivalent to the *methylphenidate group value* minus the *placebo group value*. Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

[2]Between-group difference tested using two-sample t-test with equal variance

[3]Between-group difference tested using linear regression analysis performed with adjustment for baseline fatigue severity and FACIT-Fatigue score at visit 0

Table 28 shows the number of participants in each arm reaching the MCID for the FAS (reduction of 4 points) and the FACIT-Fatigue (increase of 3 points) instruments. Similar proportions of participants in each arm met the MCID at each time point, although fewer participants who had received methylphenidate continued to meet the MCID for either FAS or FACIT-Fatigue 6 weeks after discontinuing medications (30 weeks).

Table 28 *- Number of participants, stratified by allocation arm, achieving the MCID for FAS and FACIT-Fatigue measurements of fatigue, compared with their baseline values for each instrument, at the end of each 6-week study period*

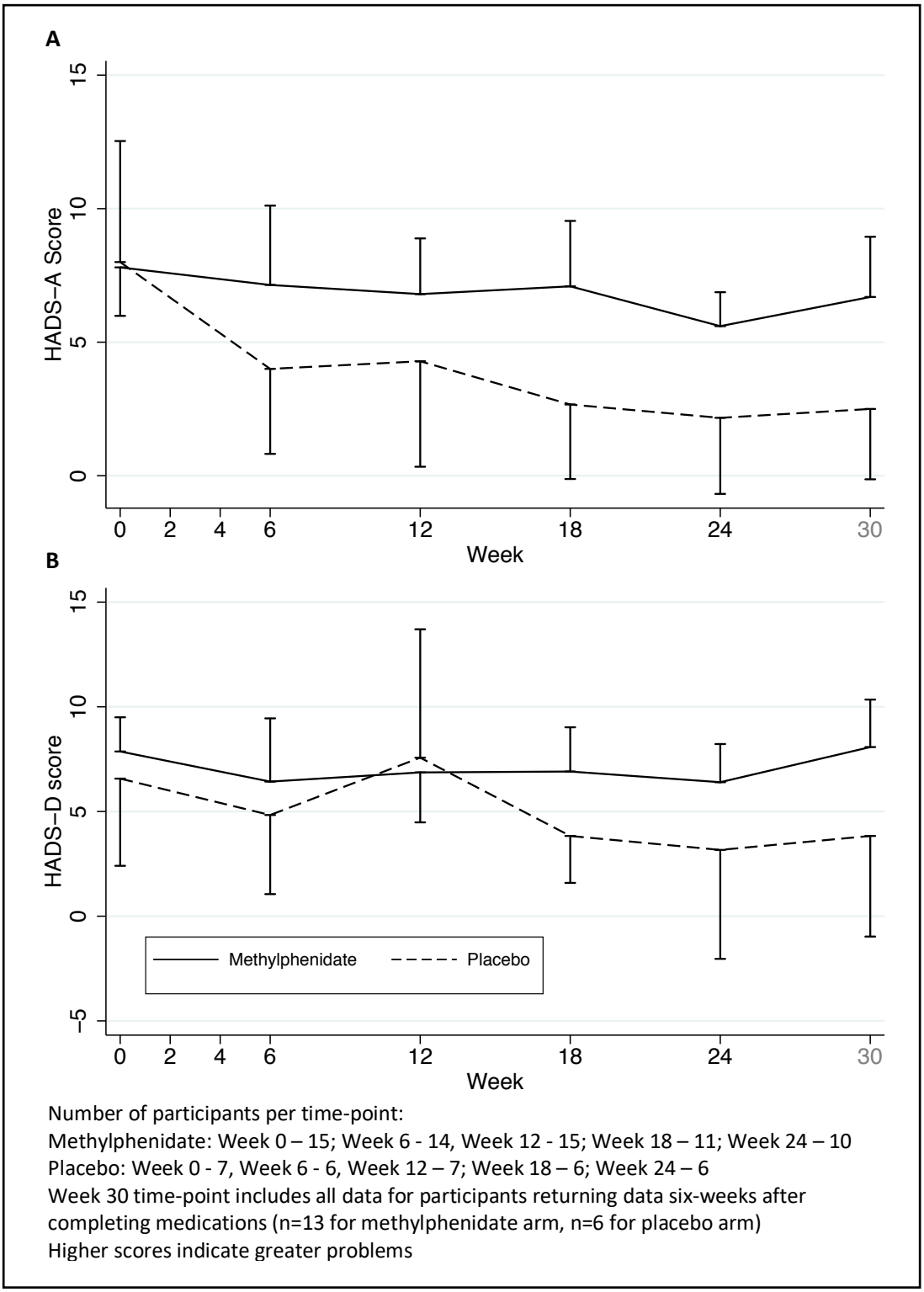
	Methylphenidate			Placebo		
Week	**n**	**FAS**	**FACIT-Fatigue**	**n**	**FAS**	**FACIT-Fatigue**
6 weeks	15	10 (66.6)	10 (66.7)	7	7 (100.0)	6 (85.7)
12 weeks	15	11 (73.3)	11 (73.3)	7	5 (71.4)	5 (71.4)
18 weeks	11	8 (72.7)	10 (90.9)	7	6 (100.0)	5 (83.3)
24 weeks	10	8 (80.0)	8 (80.0)	6	5 (83.3)	5 (83.3)
30 weeks	13	6 (46.2)	7 (53.8)	7	5 (71.4)	5 (71.4)

Anxiety and Depression

Baseline levels of anxiety symptoms were similar between groups. The mean baseline HADS-A score was 7.8 for participants allocated to methylphenidate and 8.0 for those allocated to placebo. Depression symptom scores (HADS-D) were slightly higher in the methylphenidate arm than the placebo group (7.9 vs 6.6 points).

Figure 13 shows the HADS-A and HADS-D scores recorded by each arm plotted over the course of the study. The anxiety symptoms (HADS-A) reported by the participants allocated to the placebo arm reduced over the course of the study whereas the participants who received methylphenidate did not show much reduction from baseline on average. The progression of HADS-D scores did not differ between the methylphenidate and placebo arms, with only slight changes from baseline mean differences seen at each visit.

***Figure 13** - Change in anxiety (HADS-A) scores (A) and depression (HADS-D) scores (B) over time, stratified by allocation. Results are mean values with 95% confidence intervals*



Number of participants per time-point:
Methylphenidate: Week 0 – 15; Week 6 - 14, Week 12 - 15; Week 18 – 11; Week 24 – 10
Placebo: Week 0 - 7, Week 6 - 6, Week 12 – 7; Week 18 – 6; Week 24 – 6
Week 30 time-point includes all data for participants returning data six-weeks after completing medications (n=13 for methylphenidate arm, n=6 for placebo arm)
Higher scores indicate greater problems

Both the HADS-A and HADS-D scores reduced over time in the placebo arm compared with the methylphenidate arm. Table 29 displays the data for HADS-A scores at each study visit, stratified by allocated treatment. The mean HADS-A score was between 2.5 and 4.4 points lower in the placebo arm than the methylphenidate arm, indicating a lower level of anxiety symptoms within the participants receiving placebo. This between-group difference was still present six weeks after completing trial medications (week 30). Adjustment for baseline HADS-A values showed that the between-group difference became statistically significant, in favour of the placebo group, from week 12 and remained so for the duration of the study.

***Table 29** - Anxiety symptoms measured by the Hospital Anxiety and Depression Scale – Anxiety (HADS-A) score during follow-up, including between-group differences*

	Methylphenidate		Placebo		Unadjusted difference[1,2]		Adjusted difference[1,3]	
Week	**n**	**Mean (S.D.)**	**n**	**Mean (S.D.)**	**Mean**	**95% C.I.**	**Mean**	**95% C.I.**
0	15	7.8 (3.3)	7	8.0 (4.9)	-0.2	-3.9, 3.5	-	-
6	14	7.1 (5.1)	6	4.0 (3.0)	3.1	-1.6, 7.9	1.9	-1.6, 5.3
12	15	6.8 (3.9)	7	4.3 (4.3)	2.5	-1.2, 6.3	2.7	0.4, 5.0
18	11	7.1 (3.6)	6	2.7 (2.7)	4.4	0.8, 8.1	4.3	1.8, 6.7
24	10	5.6 (1.8)	6	2.2 (2.7)	3.4	1.0, 5.8	3.4	1.6, 5.3
30	13	6.9 (3.7)	7	2.5 (2.5)	4.2	0.6, 7.8	3.6	0.6, 6.5

Higher values indicate greater reported anxiety symptoms.

[1]Mean difference is equivalent to the *methylphenidate group value* minus the *placebo group value*. Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

[2]Between-group difference tested using two-sample t-test with equal variance

[3]Between-group difference tested using linear regression analysis performed with adjustment for baseline fatigue severity and HADS-A score at visit 0

The data for HADS-D scores across the study are displayed in Table 30. The between-group difference in HADS-D score varied between -0.7 and 3.2 points whilst receiving study medications, although there was a larger between-group difference in HADS-D scores compared with HADS-A scores at baseline (week 0). After six weeks without medications, the difference between HADS-D scores had widened, with the placebo group having a lower mean HADS-D score (4.2 points lower than the methylphenidate arm). After adjustment for severity of baseline fatigue there was little difference in the mean between-group differences, although the difference is significant in favour of the placebo arm at week 18; this difference does not remain significant at week 24, though the between group difference widens in favour of the placebo arm again after participants had discontinued medications for six weeks (week 30). The results did not show such an early and sustained improvement in HADS-D scores in favour of placebo as was seen with the HADS-A values, though.

Table 30 *- Depression symptoms measured by the Hospital Anxiety and Depression Scale – Depression (HADS-D) score during follow-up, including between-group differences*

	Methylphenidate		Placebo		Unadjusted difference[1,2]		Adjusted difference[1,3]	
Week	**n**	**Mean (S.D.)**	**n**	**Mean (S.D.)**	**Mean**	**95% C.I.**	**Mean**	**95% C.I.**
0	15	7.9 (3.0)	7	6.6 (4.5)	1.3	-2.0, 4.6	-	-
6	14	6.4 (5.2)	6	4.8 (3.6)	1.6	-3.4, 6.6	0.8	-3.4, 5.0
12	15	6.9 (4.3)	7	7.6 (6.6)	-0.7	-5.6, 4.2	-1.1	-5.5, 3.3
18	11	6.9 (3.1)	6	3.8 (2.1)	3.1	-0.1, 6.2	3.2	0.5, 5.9
24	10	6.4 (2.5)	6	3.2 (5.0)	3.2	-0.8, 7.2	2.7	-1.3, 6.7
30	13	8.1 (3.8)	7	3.8 (4.6)	4.2	-0.1, 8.4	4.3	1.5, 7.1

Higher values indicate greater reported symptoms of depression.

[1]Mean difference is equivalent to the *methylphenidate group value* minus the *placebo group value*. Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

[2]Between-group difference tested using two-sample t-test with equal variance

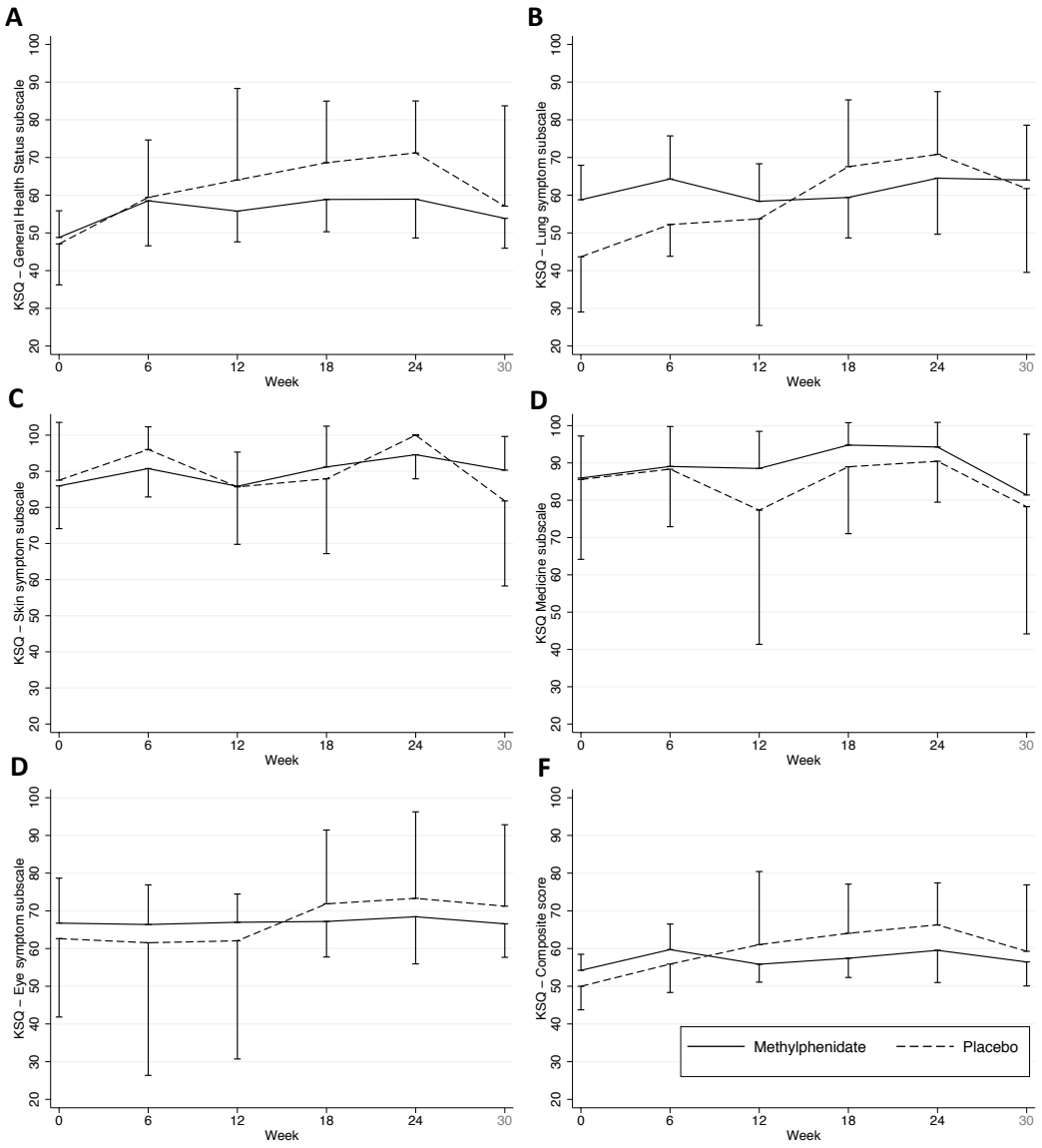
[3]Between-group difference tested using linear regression analysis performed with adjustment for baseline fatigue severity and HADS-D score at visit 0

Disease-specific health status

Scores from each subscale of the KSQ described patient-reported disease-related symptoms and health status. Baseline scores were similar for all subscales except the lung subscale; the participants allocated to placebo had lower scores than the methylphenidate group (mean score 43.7 vs 58.8, unadjusted mean difference 15.1 points), consistent with a greater burden of lung-related symptoms in the placebo group than the methylphenidate group. This was in keeping with the lower spirometry values observed in the placebo group at baseline.

The changes in scores for each KSQ subscale and the composite value are shown in Figure 14. Similar changes are seen over time for the skin, medicine, eye and composite scores (graphs C, D, E and F) over the course of the study. Slight divergence is seen in the general health status scores (graph A) between the two arms of the study after week 6; participants allocated to placebo saw an increase in this score whilst receiving medications (to week 24). This improvement was not sustained six-weeks after discontinuing medications (week 30), where no difference between the groups was seen. In the lung subscale scores (graph B), the placebo group saw an improvement in their scores over the duration of the study despite starting with a lower score than the methylphenidate group. Although there was a slight reduction in their lung subscale scores after stopping medications in the placebo arm, similar scores were seen in both arms at the end of the study, despite the placebo arm beginning with a lower mean score.

***Figure 14** - Change in disease-specific health status according to KSQ values; General health status (A), Lung (B), Skin (C), Medications (D), Eyes (E) and Composite (F) score (encompassing general health state, lung, skin, medications and eye scores). Results are mean values with 95% confidence intervals*



Number of participants per time-point:
Methylphenidate: Week 0 – 15; Week 6 – 14; Week 12 - 15; Week 18 – 11; Week 24 – 10
Placebo: Week 0, 6, 12 – 7; Week 18 – 6; Week 24 – 6
Week 30 time-point includes all data for participants returning data six-weeks after completing medications (n=13 for methylphenidate arm, n=7 for placebo arm)
Lower scores = worse disease-related symptoms/health status

The unadjusted and adjusted between-group differences for each KSQ subscale are shown in table 31 and 32. For the general health status, divergence is seen between the groups in favour of the placebo arm, with a significant difference in values seen between the groups at week 18 and increasing at week 24 when adjusted for baseline fatigue severity (mean difference -14.9 points, 95% CI -23.7, -6.2).

In the lung subscale, although both groups showed improvements in mean scores over the course of the study, the values show a narrowing of the mean difference over the course of the study. The initial mean difference was 15.1 points (unadjusted) in favour of the methylphenidate arm, narrowing over the duration of the study, with the mean difference at 24 weeks being 6.3 points (unadjusted) in favour of the placebo arm. Adjustment for baseline values increased the between-group difference in favour of the placebo group, coming close to but not achieving statistical significance compared with the methylphenidate arm.

Improvements were also seen in the composite KSQ outcome, with the adjusted analysis showing a significant improvement in favour of the placebo arm at week 12, which increased in magnitude over the remainder of the duration the participants were receiving medications; at week 24 the mean KSQ composite score was 12.4 points lower in the methylphenidate arm (95% CI -20.6, -4.2), suggesting worse disease-related symptoms and health status compared with the placebo arm. This between-group difference persisted, albeit to a lesser extent, at six weeks after discontinuing intervention.

The improvements seen in the placebo group during the 24 weeks of study medication showed some evidence of persistence compared with their baseline values. Both the placebo and methylphenidate groups saw improvements in KSQ general health status and lung scores at the end of the study compared with their baseline values, although the size of improvement was larger in the placebo group for both (10.0 vs 5.1 points and 18.1 vs 5.2 points for the lung and general health state scores respectively).

Table 31 *- Disease-related health status (general health status, lung and skin subscales) measured by the Kings Sarcoidosis Questionnaire (KSQ) during follow-up, including between-group differences*

		Methylphenidate		Placebo		Unadjusted difference[1,2]		Adjusted difference[1,3]	
	Week	n	Mean (S.D.)	n	Mean (S.D.)	Mean	95% C.I.	Mean	95% C.I.
General Health State	0	15	48.8 (12.8)	7	47.1 (11.8)	1.7	-10.2, 13.6	-	-
	6	14	58.5 (20.7)	7	59.4 (16.5)	-0.9	-19.7, 17.9	-4.0	-13.9, 6.0
	12	15	55.8 (14.7)	7	64.0 (26.2)	-8.3	-26.3, 9.8	-10.3	-21,7, 1.1
	18	11	58.9 (12.7)	6	68.6 (15.6)	-9.8	-24.6, 5.1	-9.7	-19.1, -0.2
	24	10	59.0 (14.4)	6	71.2 (13.1)	-12.3	-27.7, 3.2	-14.9	-23.7, -6.2
	30	13	53.9 (13.1)	7	57.1 (28.8)	-3.2	-22.7, 16.2	-8.8	-20.6, 3.1
Lung	0	15	58.8 (16.5)	7	43.7 (15.8)	15.1	-0.4, 30.7	-	-
	6	14	64.3 (19.8)	7	52.2 (9.1)	12.1	-4.5, 28.7	0.3	-11.7, 12.3
	12	15	58.4 (18.0)	7	53.7 (30.5)	4.7	-16.8, 26.2	-11.5	-26.7, 3.7
	18	11	59.4 (16.0)	6	67.6 (16.9)	-8.2	-25.8, 9.5	-11.7	-26.0, 2.6
	24	10	64.5 (20.8)	6	70.8 (15.9)	-6.3	-27.5, 15.0	-16.7	-33.7, 0.2
	30	13	64.0 (24.1)	7	61.8 (24.0)	2.3	-21.5, 26.0	-11.9	-31.6, 7.8
Skin	0	15	86.0 (21.4)	7	87.5 (17.3)	-1.6	-20.9, 17.8	-	-
	6	14	90.8 (13.6)	7	96.0 (6.8)	-5.3	-16.8, 6.3	-4.7	-14.9, 5.5
	12	15	85.8 (17.1)	7	85.7 (17.2)	0.2	-16.2, 16.5	0.5	-15.9, 16.9
	18	11	91.2 (16.8)	6	87.9 (19.7)	3.3	-16.0, 22.6	5.5	-9.8, 20.9
	24	10	94.6 (9.3)	6	100 (0.0)	-5.4	-13.7, 2.9	-4.4	-12.4, 3.7
	30	13	90.3 (15.4)	7	81.8 (25.4)	8.5	-10.5, 27.6	7.8	-9.2, 24.7

Higher values indicate greater health-related quality of life and lower burden of disease-related symptoms.

[1]Mean difference is equivalent to the *methylphenidate group value* minus the *placebo group value*. Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

[2]Between-group difference tested using two-sample t-test with equal variance

[3]Between-group difference tested using linear regression analysis performed with adjustment for baseline fatigue severity and KSQ subscale scores at visit 0

***Table 32** - Disease-related health status (medication and eye subscales, composite score of all subscales) measured by the Kings Sarcoidosis Questionnaire (KSQ) during follow-up, including between-group differences*

		Methylphenidate		Placebo		Unadjusted difference[1,2]		Adjusted difference[1,3]	
	Week	n	Mean (S.D.)	n	Mean (S.D.)	Mean	95% C.I.	Mean	95% C.I.
Medication	0	15	86.0 (20.3)	7	85.6 (23.2)	-0.4	-19.9, 20.7	-	-
	6	14	89.0 (18.5)	7	88.3 (16.7)	0.7	-16.7, 18.1	0.3	-12.7, 13.2
	12	15	88.5 (18.0)	7	77.3 (38.9)	11.2	-13.7, 36.1	11.1	-10.4, 32.7
	18	11	94.8 (8.9)	6	89.0 (17.1)	5.8	-7.4, 19.1	7.4	-7.2, 22.0
	24	10	94.3 (9.2)	6	90.5 (10.5)	3.8	-6.9, 14.5	4.4	-6.3, 15.1
	30	13	81.4 (27.0)	7	78.3 (36.9)	3.1	-27.0, 33.3	-0.4	-26.8, 26.0
Eye	0	15	66.7 (21.5)	7	62.6 (22.5)	4.1	-16.8, 25.0	-	-
	6	14	66.4 (18.2)	7	61.5 (28.0)	4.8	-20.5, 30.2	2.8	-12.9, 18.5
	12	15	67.0 (13.5)	7	62.1 (33.9)	4.9	-15.9, 25.7	3.0	-16.4, 22.4
	18	11	67.2 (14.0)	6	71.9 (18.6)	-4.7	-21.7, 12.3	-6.3	-21.5, 8.9
	24	10	68.4 (17.5)	6	73.3 (21.9)	-4.9	-26.1, 16.3	-6.3	-29.3, 16.7
	30	13	66.6 (14.7)	7	71.2 (23.3)	-4.7	-22.5, 13.1	-6.9	-19.4, 5.6
Composite	0	15	54.2 (7.7)	7	50.0 (6.7)	4.2	-2.8, 11.3	-	-
	6	14	59.7 (11.7)	7	55.9 (8.2)	3.8	-6.6, 14.2	-2.4	-6.9, 2.2
	12	15	55.8 (8.6)	7	61.0 (21.0)	-5.2	-18.1, 7.7	-11.1	-20.0, -2.2
	18	11	57.4 (7.6)	6	64.1 (12.4)	-6.6	-16.9, 3.6	-8.6	-15.1, -2.1
	24	10	59.5 (11.9)	6	66.3 (10.6)	-6.8	-19.5, 6.0	-12.4	-20.6, -4.2
	30	13	56.4 (10.5)	7	59.3 (19.1)	-2.8	-16.6, 10.9	-9.6	-18.0, -1.2

Higher values indicate greater health-related quality of life and lower burden of disease-related symptoms.

[1]Mean difference is equivalent to the *methylphenidate group value* minus the *placebo group value*. Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

[2]Between-group difference tested using two-sample t-test with equal variance

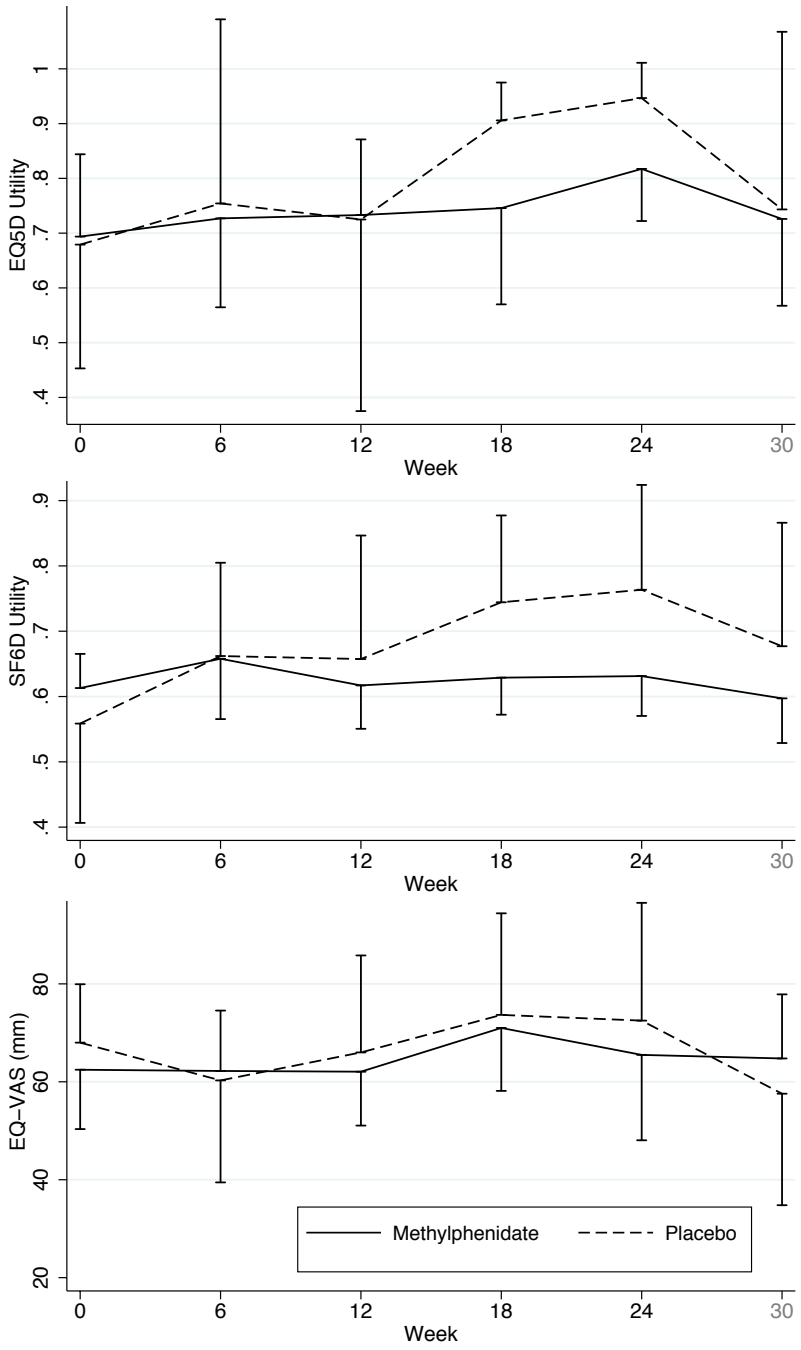
[3]Between-group difference tested using linear regression analysis performed with adjustment for baseline fatigue severity and KSQ subscale scores at visit 0

Health utility values

Health utility values were derived from the EQ5D and SF-36 data (converted to SF-6D scores for this purpose) using existing UK population conversion sets. Scores from the visual analogue scale of patient-reported health status (contained within the EQ5D questionnaire) was also included for comparison. The mean values for each measure across the study duration are shown in Figure 15. The EQ5D and SF-6D-derived utility values show differences at baseline; the mean utility values from the EQ5D questionnaires at baseline was higher in both the methylphenidate and placebo arms, by 0.081 and 0.120 respectively.

The performance of both the EQ5D and SF-6D appears similar across the study period, with an earlier divergence in SF-6D-derived values seen between the two groups compared with the EQ5D-derived values. The EQ-VAS scores do not show any difference between the two groups, with the change over time in the EQ-VAS scores appearing almost identical in the two arms.

Figure 15 *- Change in health utility scores (EQ-5D and SF-6D-derived values) and EQ-VAS score (mm). Results are mean values with 95% confidence intervals*



Number of participants per time-point:
Methylphenidate: Week 0 – 15; Week6 – 14; Week 12 - 15; Week 18 – 11; Week 24 – 10
Placebo: Week 12 – 7; Week 18 – 6; Week 24 – 6
Week 30 time-point includes all data for participants returning data six-weeks after completing medications (n=13 for methylphenidate arm, n=7 for placebo arm)
Higher scores indicate greater health related quality of life/health utility

The mean differences between the SF-6D and EQ5D utility values are shown in Tables 33 and 34. The participant-reported health status from EQ-VAS, scored between 0 and 100, are shown in table 35. Minimal differences were seen in the EQ-VAS scores across the study; adjusting for fatigue severity at baseline did not alter the results. Both the EQ5D and SF-6D utility values showed divergence between the two groups across the course of the study, with the magnitude of change similar between the two measures in the unadjusted comparison. The SF-6D-derived utility values also showed divergence between the mean difference of the two groups at an earlier time-point compared with the EQ5D-derived values, with the adjusted values for baseline SF-6D utility values showing statistically significant differences between the methylphenidate and placebo arms at 12 weeks, compared with 18 weeks for EQ5D-derived utility scores; both scores showed higher utility values in the placebo arm. A greater magnitude of difference between groups was seen in the SF-6D scores compared with the EQ5D scores.

Six weeks after discontinuing study medications, small improvements in health utility values remain compared to baseline in EQ5D-derived utility values in both the methylphenidate and placebo arms (0.032 and 0.064 respectively). The SF-6D-derived values behaved slightly differently; the placebo group maintained an improvement over baseline utility scores (0.118) whereas participants in the methylphenidate arm reported a lower utility score at 30 weeks using SF-6D values compared with baseline values (-0.016 compared with baseline). The adjusted analysis for the SF-6D showed a between-group difference at week 30 that was statistically significant, in favour of placebo, whereas the EQ5D values showed no difference between groups in either the adjusted or unadjusted analysis.

The results suggest that the two quality of life measures used behaved slightly differently within the study, both in calculated baseline health status values and the change in utility scores across the trial visits, and that these derived utility values are different to participant-reported quality of life from the EQ-VAS score.

***Table 33** - Health utility scores derived from the EQ5D instrument during follow-up, including between-group differences*

	Methylphenidate		Placebo		Unadjusted difference[1,2]		Adjusted difference[1,3]	
Week	**n**	**Mean (S.D.)**	**n**	**Mean (S.D.)**	**Mean**	**95% C.I.**	**Mean**	**95% C.I.**
0	15	0.694 (0.271)	7	0.679 (0.244)	0.015	-0.237, 0.266	-	-
6	14	0.727 (0.281)	7	0.754 (0.364)	-0.027	-0.327, 0.272	-0.036	-0.177, 0.104
12	15	0.733 (0.249)	7	0.725 (0.378)	0.008	-0.273, 0.289	-0.005	-0.121, 0.111
18	11	0.746 (0.262)	6	0.906 (0.066)	-0.160	-0.395, 0.075	-0.102	-0.195, -0.008
24	10	0.817 (0.133)	6	0.947 (0.061)	-0.129	-0.254, -0.004	-0.139	-0.214, -0.065
30	13	0.726 (0.262)	7	0.743 (0.351)	-0.017	-0.308, 0.273	-0.052	-0.209, 0.104

***Table 34** - Health utility scores derived from the SF-6D instrument during follow-up, including between-group differences*

	Methylphenidate		Placebo		Unadjusted difference[1,2]		Adjusted difference[1,3]	
Week	**n**	**Mean (S.D.)**	**n**	**Mean (S.D.)**	**Mean**	**95% C.I.**	**Mean**	**95% C.I.**
0	15	0.613 (0.094)	7	0.559 (0.164)	0.054	-0.060, 0.169	-	-
6	14	0.658 (0.160)	6	0.662 (0.154)	-0.004	-0.158, 0.149	-0.048	-0.178, 0.081
12	15	0.617 (0.120)	7	0.657 (0.204)	-0.040	-0.184, 0.103	-0.097	-0.173, -0.021
18	11	0.629 (0.084)	6	0.744 (0.127)	-0.115	-0.224, -0.007	-0.135	-0.209, -0.060
24	10	0.631 (0.085)	6	0.764 (0.153)	-0.132	-0.259, -0.006	-0.161	-0.266, -0.056
30	13	0.597 (0.108)	7	0.677 (0.204)	-0.080	-0.229, 0.070	-0.130	-0.217, -0.043

Higher values indicate greater health status (1.0 = best imaginable quality of life, 0.0 = worst imaginable quality of life; states worse than 0.0, indicating a quality of life worse than death, are possible in the EQ5D-derived values).

[1]Mean difference is equivalent to the *methylphenidate group value* minus the *placebo group value*. Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

[2]Between-group difference tested using two-sample t-test with equal variance

[3]Between-group difference tested using linear regression analysis performed with adjustment for baseline fatigue severity and utility instrument score at visit 0

***Table 35** - Participant-reported quality of life taken from the EQ-VAS instrument (within EQ5D) during follow-up, including between-group differences*

	Methylphenidate		Placebo		Unadjusted difference[1,2]		Adjusted difference[1,3]	
Week	**n**	**Mean (S.D.)**	**n**	**Mean (S.D.)**	**Mean**	**95% C.I.**	**Mean**	**95% C.I.**
0	15	62.5 (21.9)	7	68.0 (12.9)	-5.5	-24.3, 13.2	-	-
6	14	62.2 (21.4)	6	60.3 (22.5)	1.9	-19.1, 23.0	2.9	-16.8, 22.7
12	15	62.1 (19.9)	7	66.0 (21.4)	-3.9	-23.4, 15.5	-3.6	-20.9, 13.6
18	11	71.0 (19.1)	6	73.7 (19.8)	-2.7	-23.6, 18.3	-3.3	-19.7, 13.1
24	10	65.5 (24.4)	6	72.5 (22.9)	-7.0	-33.4, 19.4	-7.6	-32.4, 17.2
30	13	64.3 (20.9)	7	57.6 (24.6)	7.2	-15.1, 29.5	4.5	-10.7, 19.6

Higher values indicate greater perceived health (100 = best imaginable quality of life, 0 = worst imaginable quality of life).

[1]Mean difference is equivalent to the *methylphenidate group value* minus the *placebo group value*. Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

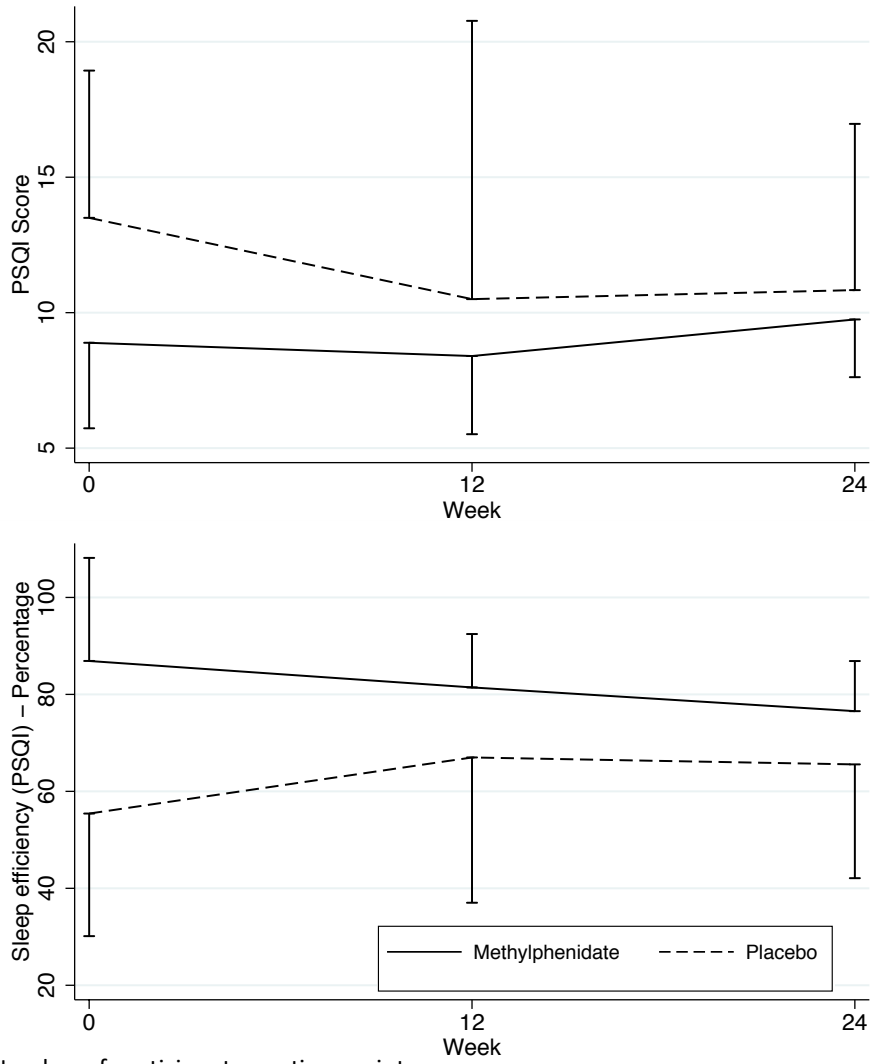
[2]Between-group difference tested using two-sample t-test with equal variance

[3]Between-group difference tested using linear regression analysis performed with adjustment for baseline fatigue severity and utility instrument score at visit 0

Sleep quality

Sleep quality through the trial was scored using the PSQI questionnaire and an assessment of sleep quality. Figure 16 shows the changes in sleep quality and PSQI scores for each group across the duration of the study. The number of data-points at each time point are lower than other measures as not all participants completed the PSQI questionnaire; the addition of this instrument occurred following a substantial amendment in April 2017, by which time nine participants had entered the study, two of which had completed all study visits.

Figure 16 *- Change in PSQI score and sleep efficiency (percentage of night asleep). Results are mean values with 95% confidence intervals*



Number of participants per time-point:
Methylphenidate: Week 0 - 9; Week 12 – 10; Week 24 – 8
Placebo: Week 12 – 4; Week 18 – 4; Week 24 – 6
Sleep efficiency – higher values = better sleep; PSQI Score – lower values = better sleep

Sleep quality was worse at baseline in participants allocated to placebo, with higher mean PSQI scores and lower sleep efficiency compared with the methylphenidate group. Sleep quality and efficiency showed very slight worsening of values in the methylphenidate group although a modest improvement in sleep quality was seen in the placebo group. Sleep efficiency showed a modest increase in the placebo group, which was maintained to week 24. Tables 36 and 37 show the mean scores at each visit for both PSQI scores and sleep efficiency, as well as between-group differences (both unadjusted values and adjusted for baseline scores). No significant differences were seen between groups for either PSQI or sleep efficiency, although when adjusted for baseline values the placebo group saw small improvements in sleep quality (both PSQI and sleep efficiency) as the study progressed, relative to the methylphenidate group.

The results suggest that methylphenidate use did not have a marked negative impact in sleep quality for participants in the study, either compared to the placebo group performance or relative to baseline values of sleep quality and efficiency.

***Table 36** - Subjective sleep quality, taken from the PSQI instrument during follow-up, including between-group differences*

	Methylphenidate		Placebo		Unadjusted difference[1,2]		Adjusted difference[1,3]	
Week	**n**	**Mean (S.D.)**	**n**	**Mean (S.D.)**	**Mean**	**95% C.I.**	**Mean**	**95% C.I.**
0	9	8.9 (4.1)	4	13.5 (3.4)	-4.6	-9.8, 0.6	-	-
12	10	8.4 (4.0)	4	10.5 (6.5)	-2.1	-8.2, 4.0	4.4	-3.2, 11.9
24	8	9.8 (2.5)	6	10.8 (5.8)	-1.1	-6.1, 3.9	0.9	-23.3, 25.1

Higher values indicate worse perceived sleep quality

[1]Mean difference is equivalent to the *methylphenidate group value* minus the *placebo group value*. Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

[2]Between-group difference tested using two-sample t-test with equal variance

[3]Between-group difference tested using linear regression analysis performed with adjustment for baseline fatigue severity and PSQI score at visit 0

***Table 37** - Sleep efficiency (percentage of the time in bed spent asleep) during follow-up, including between-group differences*

	Methylphenidate		Placebo		Unadjusted difference[1,2]		Adjusted difference[1,3]	
Week	**n**	**Mean (S.D.)**	**n**	**Mean (S.D.)**	**Mean**	**95% C.I.**	**Mean**	**95% C.I.**
0	9	86.9 (27.6)	4	55.4 (15.9)	31.5	-1.6, 64.5	-	-
12	10	81.4 (15.4)	4	67.0 (18.8)	14.4	-6.6, 35.5	-12.4	-40.3, 15.4
24	8	76.5 (12.4)	6	65.6 (22.4)	11.0	-9.3, 31.3	1.6	-64.7, 68.0

Higher values indicate better sleep efficiency (higher percentage of the time in bed spent asleep)

[1]Mean difference is equivalent to the *methylphenidate group value* minus the *placebo group value*. Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

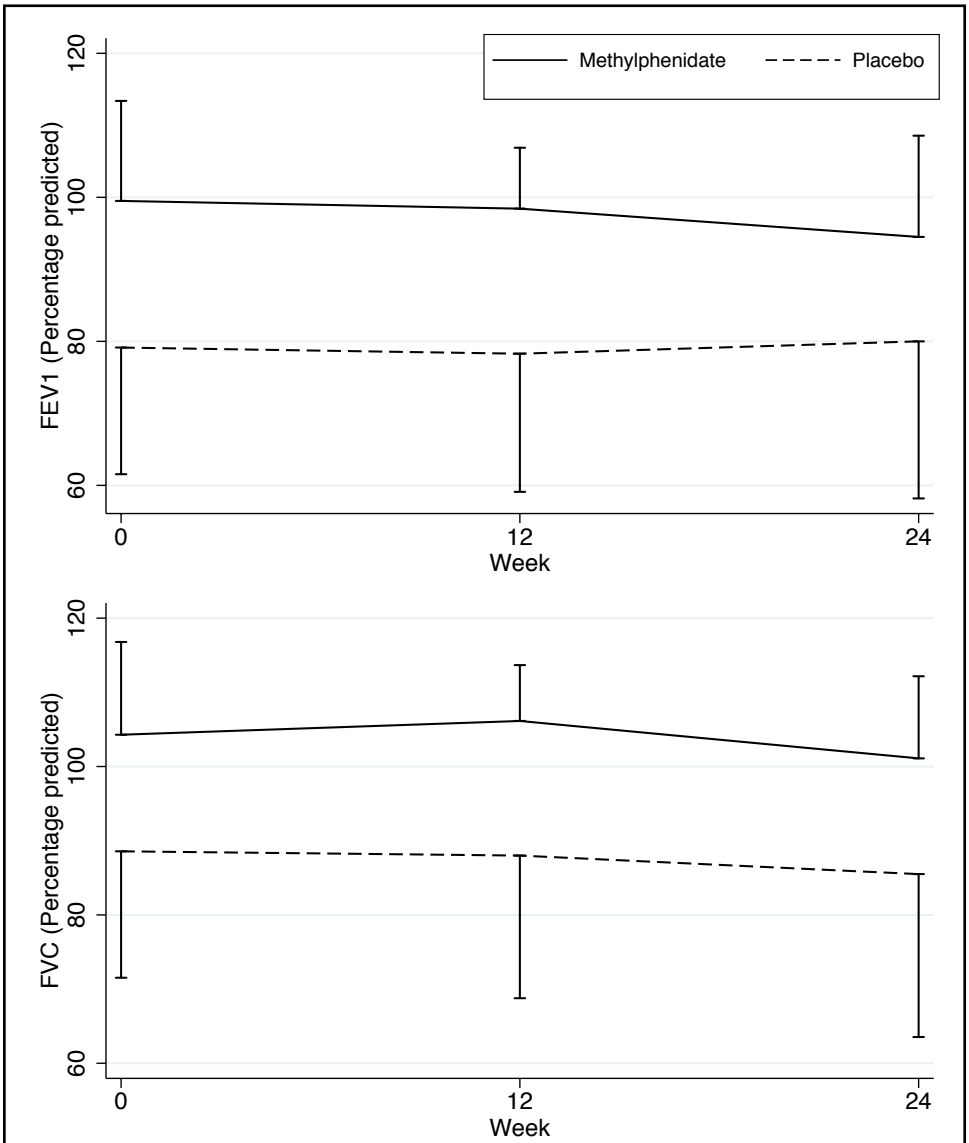
[2]Between-group difference tested using two-sample t-test with equal variance

[3]Between-group difference tested using linear regression analysis performed with adjustment for baseline fatigue severity and sleep efficiency at visit 0

Spirometry and Exercise (MSWT)

Figure 17 displays the progression of spirometry results for each group over the course of the study. No significant changes were seen for either FEV1 or FVC over the duration of the study in either group, although values for both the measurements were lower at baseline in the placebo group compared with the methylphenidate group.

Figure 17 *- Change in Forced Expiratory Volume in 1 second (FEV1) and Forced Vital Capacity (FVC) values during the trial. Results are mean values with 95% confidence intervals*



Number of participants per time-point:
Methylphenidate: Week 0 - 14; Week 12 – 10; Week 24 – 10
Placebo: Week 12 – 7; Week 18 – 6; Week 24 – 6

Tables 38 and 39 show the mean values in each group alongside between-group differences. Although the FEV1 and FVC values were markedly higher in the methylphenidate group than the placebo group, no significant difference existed between them in the adjusted analysis.

Table 38 *- Forced Expiratory Volume in 1 second (FEV1) during follow-up, including between-group differences. Values are percentages of predicted values*

	Methylphenidate		Placebo		Unadjusted difference[1,2]		Adjusted difference[1,3]	
Week	**n**	**Mean (S.D.)**	**n**	**Mean (S.D.)**	**Mean**	**95% C.I.**	**Mean**	**95% C.I.**
0	14	99.5 (24.1)	7	79.1 (19.0)	20.4	-1.5, 42.2	-	-
12	10	98.4 (14.6)	6	78.3 (20.7)	20.1	3.9, 36.4	8.2	-2.2, 18.6
24	10	94.5 (19.6)	6	80.0 (20.8)	14.5	-7.7, 36.7	6.4	-6.6, 19.3

[1]Mean difference is equivalent to the *methylphenidate group value* minus the *placebo group value*. Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

[2]Between-group difference tested using two-sample t-test with equal variance

[3]Between-group difference tested using linear regression analysis performed with adjustment for baseline fatigue severity and FEV1 at visit 0

Table 39 *- Forced Expiratory Volume in 1 second (FEV1) during follow-up, including between-group differences. Values are percentages of predicted values*

	Methylphenidate		Placebo		Unadjusted difference[1,2]		Adjusted difference[1,3]	
Week	**n**	**Mean (S.D.)**	**n**	**Mean (S.D.)**	**Mean**	**95% C.I.**	**Mean**	**95% C.I.**
0	14	104.3 (21.7)	7	88.6 (18.4)	15.7	-4.3, 35.8	-	-
12	10	106.1 (13.0)	6	88.0 (20.8)	18.1	2.7, 33.5	8.2	-1.5, 18.0
24	10	101.1 (15.5)	6	85.5 (20.9)	15.6	-3.9, 35.1	10.9	-1.4, 23.3

[1]Mean difference is equivalent to the *methylphenidate group value* minus the *placebo group value*. Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

[2]Between-group difference tested using two-sample t-test with equal variance

[3]Between-group difference tested using linear regression analysis performed with adjustment for baseline fatigue severity and FVC at visit 0

The results from exercise capacity assessment across the study, performed using the MSWT. A number of participants were unable to perform all three measurements due to a loss of suitable facilities for performing the MSWT; in total, ten data-points were missing for this reason (16.7% of all MSWTs that should have been undertaken). Only eleven participants were able to provide MSWT measurements at week 24. As a result, only sixteen participants performed at least two MSWT values.

Between group differences for MSWT distances at weeks 0, 12 and 24 are shown in Table 40. Although the methylphenidate group managed 100m further on average at baseline compared with the placebo group, this difference gradually increased according to the unadjusted analysis, with the mean between-group difference reaching 191.8m at week 24. When adjusted for baseline distance and severity the difference between groups remained in favour of the methylphenidate group, albeit by a reduced margin; the mean difference was 43.9m in favour of the methylphenidate group in the adjusted analysis. The change in mean scores is shown graphically in Figure 18.

***Table 40** - Modified Shuttle Walk (MSWT) distances (in metres) during follow-up, including between-group differences*

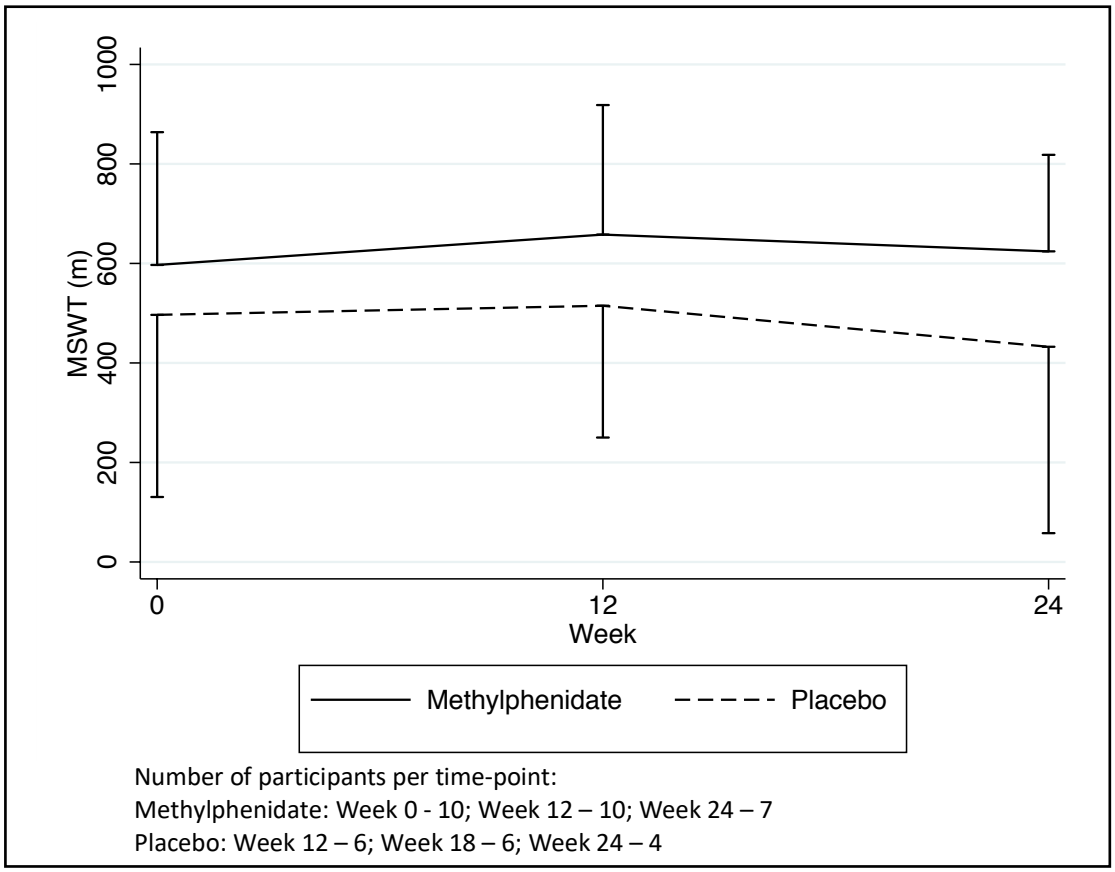
	Methylphenidate		Placebo		Unadjusted difference[1,2]		Adjusted difference[1,3]	
Week	**n**	**Mean (S.D.)**	**n**	**Mean (S.D.)**	**Mean**	**95% C.I.**	**Mean**	**95% C.I.**
0	10	597.0 (373.0)	6	496.7 (348.8)	100.3	-303.4, 504.1	-	-
12	10	658.0 (397.7)	6	515.0 (252.4)	143.0	-220.8, 506.8	56.4	-73.9, 186.6
24	7	624.3 (430.3)	4	432.5 (235.4)	191.8	-118.2, 501.8	43.9	-216.3, 304.1

[1]Mean difference is equivalent to the *methylphenidate group value* minus the *placebo group value*. Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

[2]Between-group difference tested using two-sample t-test with equal variance

[3]Between-group difference tested using linear regression analysis performed with adjustment for baseline fatigue severity and MSWT at visit 0

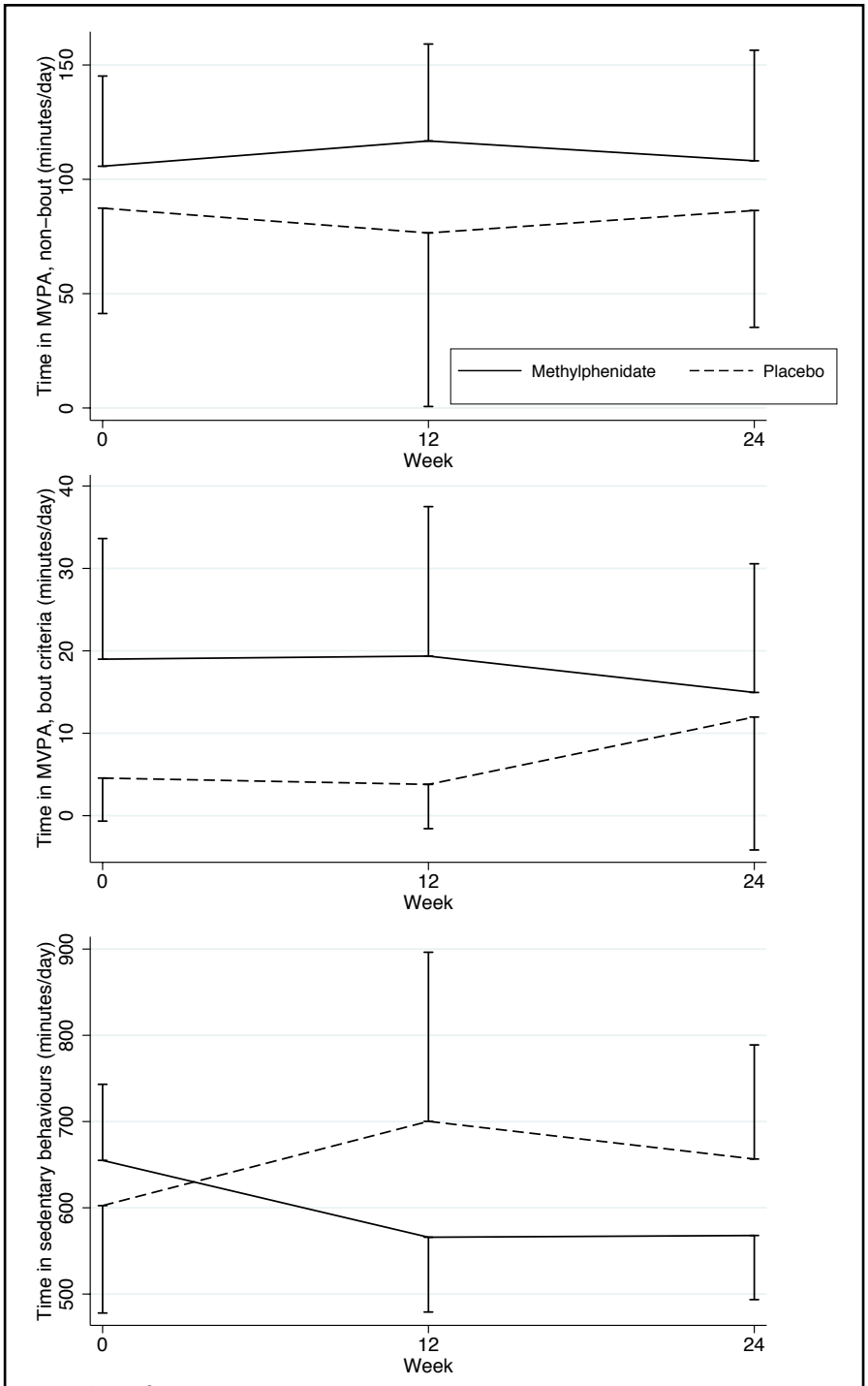
***Figure 18** - Change in MSWT distance during the trial. Results are mean values with 95% confidence intervals for participants providing at least two values during the study*



Activity

Daily time in MVPA at baseline was similar between groups, although the methylphenidate group spent a greater period of time in MVPA according to WHO-criteria. Over the duration of the study the time spent per day in MVPA did not change in either group, although a small increase was seen in the daily time in MVPA according to WHO "bout" criteria in the placebo group compared with baseline. The placebo group spent less time than the methylphenidate group per day in sedentary behaviours (any activity involving sitting, reclined or lying flat) at baseline, but spent longer periods of time in sedentary behaviours in the later recording periods. By contrast, the methylphenidate group spent less time in sedentary behaviours as the study progressed. The change in activity levels during the study are shown in Figure 19.

***Figure 19** - Changes in GENEActiv-recorded activity levels (MVPA), daily time in MVPA according to World Health Organisation recommendations on activity, and daily time in sedentary behaviours) during the study*



Number of participants per time-point:
Methylphenidate: Week 0 – 14; Week 12 – 15; Week 24 - 9
Placebo: Week 0 – 6; Week 12 – 4; Week 24 – 6
Bout criteria = >80% of any 10-minute period must be above threshold for Moderate and Vigorous Physical Activity (MVPA)

The mean values for the activity outcomes, including between-group differences, are shown in tables 41, 42 and 43. The methylphenidate group spent longer periods performing at least moderate activity over the duration of the study, spending on average between 18.3 and 40.2 more minutes per day in MVPA than the placebo group; this was also true when using WHO-criteria to define valid time in MVPA, although both groups spent less time in MVPA using these criteria. The adjusted analysis reduced the mean-difference between the two groups.

Despite the methylphenidate group spending slightly more time per day in MVPA than the placebo group, the baseline average duration of sedentary behaviours was also higher in the methylphenidate group than placebo. Over the duration of the study the methylphenidate group spent less time in sedentary behaviours than the placebo group (Table 44); after 12 weeks, participants allocated to the methylphenidate arm spent on average 134.4 minutes less time in sedentary behaviours per day than those in the placebo arm; this between-group difference increased when adjusted for baseline levels of sedentary behaviours, with the methylphenidate group spending a significantly shorter duration in sedentary activities per day at 12 weeks (-167.3 minutes, 95% CI -320.9, -13.8 minutes per day).

Table 41 *- Daily time in MVPA (minutes); mean values for each group, with unadjusted between-group difference and adjusted for baseline fatigue severity*

	Methylphenidate		Placebo		Unadjusted difference[1,2]		Adjusted difference[1,3]	
Week	**n**	**Mean (S.D.)**	**n**	**Mean (S.D.)**	**Mean**	**95% C.I.**	**Mean**	**95% C.I.**
0	14	105.7 (68.3)	6	87.4 (43.9)	18.3	-45.7, 82.4	-	-
12	15	116.8 (76.6)	4	76.6 (47.7)	40.2	-45.6, 126.1	14.7	-29.1, 58.6
24	9	108.1 (62.9)	6	86.4 (48.7)	21.7	-44.1, 87.6	24.6	-16.8, 65.9

Table 42 *- Daily time in MVPA (minutes) using WHO bout criteria; mean values for each group, with unadjusted between-group difference and adjusted for baseline fatigue severity*

	Methylphenidate		Placebo		Unadjusted difference[1,2]		Adjusted difference[1,3]	
Week	**n**	**Mean (S.D.)**	**n**	**Mean (S.D.)**	**Mean**	**95% C.I.**	**Mean**	**95% C.I.**
0	14	19.0 (25.4)	6	4.6 (5.0)	14.4	-7.8, 36.7	-	-
12	15	19.4 (32.8)	4	3.8 (3.4)	15.6	-19.8, 50.9	-0.2	-22.3, 21.9
24	9	15.0 (20.3)	6	12.0 (15.4)	3.0	-18.2, 24.1	-6.7	-27.2, 13.8

Table 43 *- Daily time in sedentary behaviours (minute); mean values for each group, with unadjusted between-group difference and adjusted for baseline fatigue severity*

	Methylphenidate		Placebo		Unadjusted difference[1,2]		Adjusted difference[1,3]	
Week	**n**	**Mean (S.D.)**	**n**	**Mean (S.D.)**	**Mean**	**95% C.I.**	**Mean**	**95% C.I.**
0	14	665.0 (152.7)	6	602.5 (118.7)	52.5	-95.3, 200.2	-	-
12	15	565.9 (156.6)	4	700.2 (123.2)	-134.4	-313.9, 45.2	-167.3	-320.9, -13.8
24	9	567.9 (96.7)	6	656.5 (126.1)	-88.6	-212.7, 35.4	-139.2	-341.4, 63.0

[1]Mean difference is equivalent to the *methylphenidate group value* minus the *placebo group value*. Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

[2]Between-group difference tested using two-sample t-test with equal variance

[3]Between-group difference tested using linear regression analysis performed with adjustment for baseline fatigue severity and daily time in sedentary behaviours

Exit questionnaire data

Trial perception

Participants reportedly favourably on their experience of the study. The results from the exit questionnaire, administered to 19 participants after approval was given for the substantial amendment in April 2017 (after 3 participants had already completed the study), show that participants found the study to be useful and would be willing to participate in similar studies in the future. A greater number of participants who had received methylphenidate wished to continue the study medications if the option to continue them had been available compared with those in the placebo arm (91.7% vs 71.4%). The results from the exit questionnaire suggest that the high number of visits was not too arduous for participants, although data was not collected from eligible patients who declined to participate. Table 44 shows the data from the exit questionnaire.

Table 44 *- Exit questionnaire responses by treatment allocation*

Exit Question	Methylphenidate (n=12)	Placebo (n=7)
If you were given the choice to continue receiving the study medication, would you want to?	11 (91.7)	5 (71.4)
Did you find participation in the study useful?	12 (100)	7 (100)
Given the chance again, would you still have taken part in this study?	12 (100)	7 (100)
Would you recommend taking part in any future study investigating methylphenidate to other patients?	12 (100)	7 (100)

Impression of treatment allocation

Both the participants and the investigator were required to predict the assigned allocation group at the final participant visit (week 24); the participants were not informed of the investigator's thoughts. Overall, the participants were able to predict with greater accuracy their true allocation group; 18 participants (81.8%)

correctly predicted their allocation, compared with the investigator who correctly determined the allocated intervention for 16 participants (72.7% accuracy). The participants who received methylphenidate predicted their allocation with greater accuracy; 14 participants (93.3%) allocated to methylphenidate correctly determined their allocation whilst the investigator correctly predicted the allocation of 11 participants (73.3%). The results were reversed for the placebo group; the investigator correctly predicted the allocation for 5 of the 7 participants (71.4%) compared with 4 of the participants (57.1%) correctly determining their allocation to the placebo arm. The results suggest that blinding of the trial team, including the investigator, and participants, is feasible when using methylphenidate in a double-blind, parallel-arm study.

5.3 Discussion

This study, performed as a double-blind, parallel-arm, placebo-controlled trial, reported outcomes for 22 participants with sarcoidosis and associated fatigue who were randomised to receive either methylphenidate or placebo for up to 24 weeks, with the primary aim of determining the feasibility of performing future studies powered to determine the clinical efficacy of interventions for sarcoidosis-associated fatigue. The results suggest that while performing such a trial is feasible, there are important findings that must be considered when designing and implementing any follow-up studies to *FaST-MP*.

The exploratory efficacy outcomes suggested that no difference was seen between the methylphenidate and placebo arms, with between-group differences slightly favouring the placebo arm relating to improvements in fatigue, anxiety, disease-related health status and quality of life. The study was not powered to detect clinical differences between groups, but the lack of any signal to suggest benefit for methylphenidate was surprising. The clinical results seen may relate to several factors, including the chosen inclusion criteria for study participants, changes made to the study design during review by the research ethics committee, choice of dose ranges for the intervention, and possible issues with the chosen fatigue outcomes

that may have failed to identify changes in the methylphenidate group. The results also reinforce the multifactorial nature of fatigue; the use of methylphenidate for patients with chronic fatigue related to sarcoidosis should only be considered as part of the management strategy when treating such patients in clinic.

Trial interpretation

Recruitment and retention – The final recruitment total, and the monthly recruitment rate, was lower than originally anticipated. Despite originally anticipating a recruitment rate of 2-3 participants per month, the overall recruitment rate was 1.3 participant per month, necessitating extension of the recruitment period. Although the study did not recruit the full number of participants that were able to be randomised, the 22 participants that did receive study medications represented 73.3% of the recruitment target (30 patients). The 22 participants also represented 36.5% of potentially eligible patients who were approached during the study. It was initially anticipated that a greater proportion of eligible patients would wish to participate, given the lack of widely-used interventions for sarcoidosis-associated fatigue and the known impact upon quality of life when present (170). The reasons for declining participation varied, although several patients declined due to the practicalities of taking part, specifically the number of visits entailed and the distance to travel to each visit. These factors could be improved in a future study with design changes, potentially increasing the likelihood of eligible patients agreeing to participate.

Although some aspects of trial design deterred patients from participating, those who entered the study reported a positive experience of taking part according to the exit questionnaire results. Participant retention was high, with all trial subjects completing the study and no drop-outs occurring. This may be a positive aspect of the amount of participant contact with the study team, and a lower number of study visits may increase the likelihood of participants withdrawing during the study. When considering any future study, efforts to reduce the number of hospital visits must be undertaken to maximise the likelihood of patients agreeing to

participate, but ongoing contact or ease of contacting the study team must also be considered to maintain high levels of participant retention. Using alternative means of contacting participants other than bringing them to study visits, such as phone calls or electronic means of communication, may be able to improve recruitment rates whilst maintaining high participant retention.

Adherence – Throughout the study adherence to medications was excellent. All participants in the methylphenidate group and all but one of the placebo group met an adherence level of ≥80%, with median adherence levels of 99% in the methylphenidate group and 98% in the placebo group, suggesting that the use of short-acting medications requiring twice-daily dosing is feasible; this schedule also allows for more tailoring to individual needs compared with long-acting preparations. Participants also reliably returned unused study medications at the end of the study – there was no evidence of participants stockpiling or holding back medications during the study. This adherence may also relate to frequent contact with the study team, either in person or via telephone, as well as the small gel capsule size used to over-encapsulate the tablet (size 0) which enabled easy swallowing of the medication.

Safety – Methylphenidate appeared well-tolerated and safe during this study, although this conclusion is limited by the small number of participants. No participants were withdrawn due to ECG changes, which were monitored throughout the study, and although one participant discontinued medications due to cardiac-type chest pain, subsequent investigations did not identify any cardiac problems. Reported adverse events were all in keeping with the known common side effects of methylphenidate, including anxiety or cough. Although nausea was common, this most frequently occurred when medications were taken without food; participants were subsequently advised to take their morning dose with breakfast, which led to resolution of symptoms in most cases. No changes in blood pressure or pulse rate were observed over the duration of the study, either relative to baseline values or compared with changes observed in the placebo arm, suggesting that methylphenidate is safe from this aspect. One observed effect in the methylphenidate arm was a modest reduction in weight from baseline, a known

side-effect of the drug but one which would need to be monitored in future studies. Only one serious adverse event occurred which was in the methylphenidate arm but was unrelated to the medication. Overall, the medication was well-tolerated by participants over the study period and no concerns relating to safety, or the ability to identify adverse events when they did occur, were identified. This finding gives reassurance that fewer patient visits are required in future studies investigating methylphenidate as less monitoring is likely to be required given the low rate of significant adverse events occurring here.

Blinding – Neither participants nor investigator were able to correctly predict the allocation group for all participants, although prediction of allocation was able with a good degree of accuracy overall. More than three-quarters of participants (81.8%) were able to correctly predict their allocated group at the end of their time receiving study medications, with slightly lower accuracy achieved by the investigator (72.7%). Participants were more likely to be accurate in their prediction if they had been allocated to methylphenidate and the investigator was more likely to be accurate if the participant had been allocated to placebo. This suggests that, whilst blinding can be maintained to an extent, participants are able to distinguish if they are receiving methylphenidate, either due to the clinical efficacy or the side effects of the medication. The importance of this finding is that it reinforces that a cross-over design is inappropriate for investigating neurostimulants; participants can determine when they are receiving the medication with high levels of accuracy, therefore they are likely to be able to break blinding in the period of a cross-over study where the active medication is being given. The level of accuracy in predicting placebo allocation by participants was barely more than 50% in this study but would likely be much higher in a cross-over study where a period on methylphenidate would effectively break blinding for the placebo arm. Therefore, any future study requiring blinding would need to be parallel-arm not cross-over in design.

Activity monitoring and exercise outcomes – The use of activity monitors as a potential outcome measure appears to be feasible based on the high return rates of devices. Only one device was lost during return to the study team out of 60 wear

periods (1.7% of all wear periods), although four participants (6.7%) did not return any data (zero wear time) and a further three participants did not wear the device for sufficient duration to record valid levels of data; in total, 54 wear periods (90.0% of all wear periods) yielded valid data for analysis. It is unclear how the 98.3% device return rate compares with other large-scale studies utilising activity monitors, such as NHANES or UK Biobank, but it is reassuring that using pre-paid postal methods to return the accelerometer devices was reliable and suggests that it is feasible to use these devices in any future study.

In contrast to the feasibility of using the activity monitors, the use of the MSWT as a clinic-based measure of exercise capacity appeared less likely to be feasible for future trials; if it were to be used as an outcome measure then it would be important to clarify that potential sites have sufficient space to perform a MSWT. This finding is due to the difficulty in having reliable access to a safe and appropriate space to undertake the test. As the MSWT is a maximal effort test, requiring participants to increase their speed along the course to the point of running, a large amount of dedicated space is required to safely undertake the test. During the course of the *FaST-MP* study the facilities we were able to use for the MSWT were removed due to a change in the research department's location. Despite searching for an alternative location, no appropriate facilities were identified within the Norfolk and Norwich University Hospital. As we could not expect other sites to have access to dedicated facilities for an MSWT in any future study, the need for outcomes like the MSWT should be considered; there was evidence to support increased maximal effort on exercise tests from the data collected here, albeit limited by the reduced amount of data collected, and so the use of a laboratory-based test, using a treadmill or ergometer, is likely to be more feasible than performing MSWTs at NHS sites.

Clinical outcomes – This study was not powered to detect clinical differences between groups. An analysis of the clinical data collected was performed to explore how the outcome measures changed within the study, although it is important to interpret these findings with caution and use them to raise questions for future work to investigate further.

Both the methylphenidate and placebo groups showed reductions in fatigue scores from baseline, with most participants in both arms showing improvements in both FAS and FACIT-Fatigue in excess of the MCID for each instrument. Despite this, the magnitude of the improvement was larger in the placebo group than the methylphenidate group, albeit a non-significant difference from the methylphenidate arm. The placebo group also showed improvements in anxiety and depression scores (HADS-A and HADS-D) compared with those allocated to methylphenidate. There were also improvements seen in disease-related health status, with the participants randomised to placebo showing improvements in the lung and general health status sub-scores of the KSQ. The improvements in all these factors were reflected in the health utility scores derived from the EQ5D and SF-6D results, with mean improvements in health utility scores favouring the placebo arm over the methylphenidate arm. In all cases there appeared to be persistence of effect over the full study duration. The between-group differences are in contrast to previous data (173), although this is from a short cross-over study which may have been affected by the issues related to blinding, discussed above.

Although the between-group differences rarely reached significance, and the study was never powered to detect clinical difference between study arms in any of the outcomes, the performance of the placebo arm was unexpected. A number of potential elements were identified that may explain why participants allocated to methylphenidate performed no better than placebo:

- The trial design was changed at the point of review by the research ethics committee; the initial design envisaged a similar first 12 weeks of the study, with close monitoring of participants for adverse events and to allow dose titration of the study medication. At week 12 participants would then be dispensed a 12-week supply of medication and not be reviewed between week 12 and 24 unless any issues arose, so that this second half of the study period was a closer mirror of usual clinical practice. In the process of gaining ethical approval, changes had to be made to introduce increased clinical contact, specifically the between-visit phone calls and the additional visit at week 18. These changes drastically increased the amount of clinical contact

for participants within the study and potentially led to increased "quality" of interaction with the research team, an acknowledged factor that can be "extremely influential in patient outcomes [and] may be more important than specific treatment," conclusions which are based on work from studies investigating pain (287, 288). As a result, no "usual care" group existed within the trial, given that the frequency of contact that both groups had with the study team was far in excess of the usual extent of clinical contact in the outpatient clinic and may be considered an intervention itself.

- The placebo group saw marked improvements in both anxiety scores, possibly as a direct result of the factor discussed above relating to a lack of a "usual care" arm. The methylphenidate group did not see such changes; in contrast to the placebo group, scores in the HADS-A questionnaire did not change over the duration of the study. Anxiety and depression are known to be moderators of fatigue scores in patients with sarcoidosis (122); the significant reduction in anxiety may have led to reductions in fatigue levels. Furthermore, a study published following the conclusion of the *FaST-MP* trial reinforced the impact of emotional distress and anxiety about physical concerns, identifying these factors as strongly influencing fatigue scores in a small cohort of patients with sarcoidosis in Poland (289).
- The dose range was chosen based on previous research using dexmethylphenidate for sarcoidosis which used the equivalent dose range (173). However, higher doses can be used. Some participants within the methylphenidate reported only small benefits, yet tolerated the medication with only mild or transient adverse events, so having the option of using a higher daily dose (30mg twice daily) may have been beneficial for these participants.
- The inclusion criteria were broad to enable participants with sarcoidosis and significant fatigue to participate. No cut-off was specified for the duration of disease at the point of entering the study; this was primarily done to ensure that patients who had endured significant delay in reaching a diagnosis of sarcoidosis were eligible if they suffered chronic symptoms. The consequence of this was that a number of participants had been diagnosed

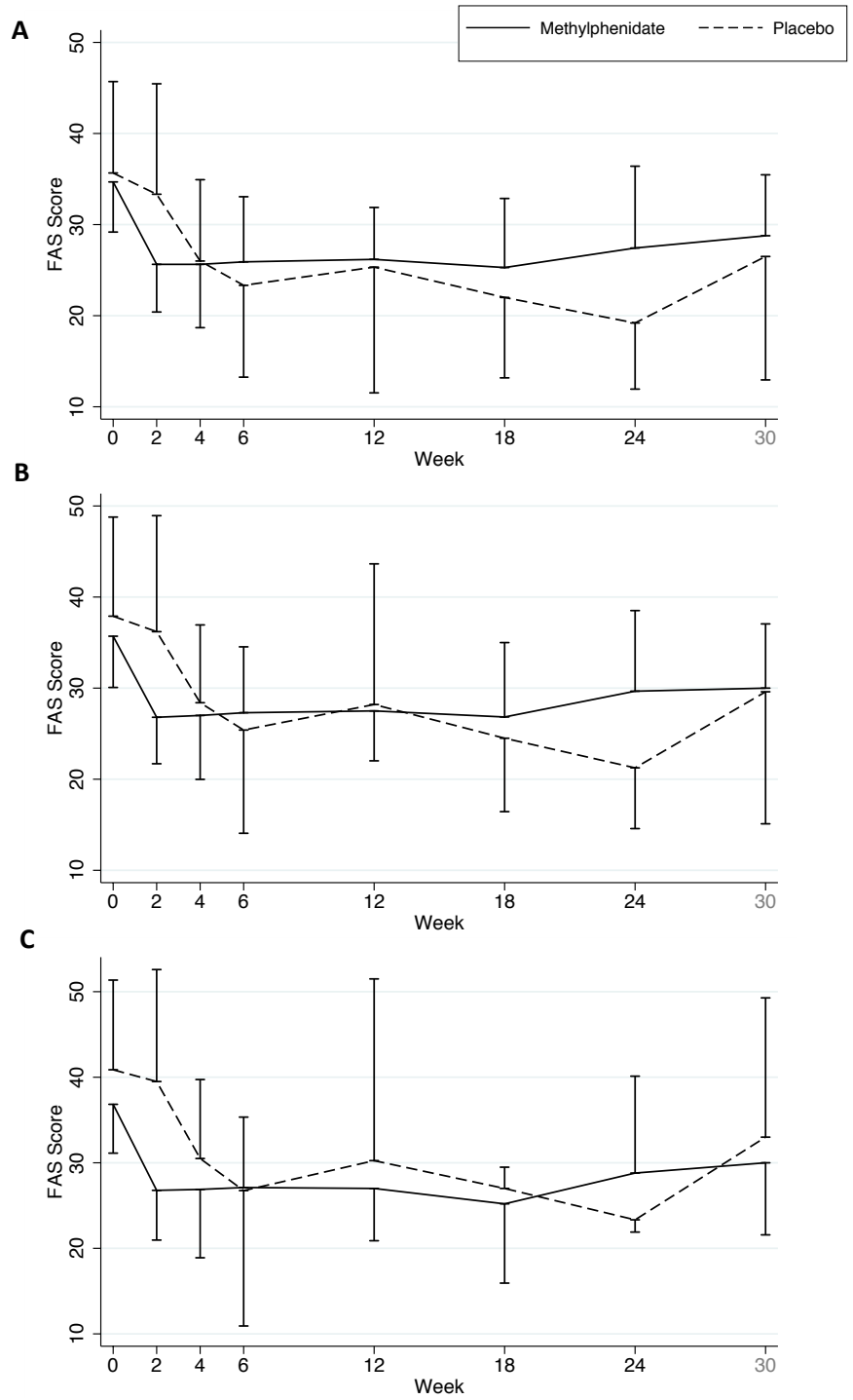
with the disease for less than a year. For some patients, fatigue may improve over time, and so including only participants diagnosed for at least a year (17 of the 22 participants in the study (77.3%) met this criteria) may have ensured only patients with chronic, non-resolving fatigue were included.

- The level of sedentary behaviour per day in the methylphenidate group decreased during the study, whereas it increased in the placebo group, with a large difference between the groups, most markedly at the 12-week stage. There was a large amount of variability seen in the reported durations of sedentary behaviour, and the number of data points is small, but the results could suggest that the methylphenidate group performed more activity than those allocated to placebo during the study. This increased activity may have meant performing more usual daily activities, and their increased fatigue levels resulted from them accomplishing more and becoming physically fatigued. The data collected here is unable to determine if this occurred, but future studies may be able to incorporate better methods of recording this such as an activity diary or a formalised activity record such as the National Institute of Health (NIH) activity record (290).
- Only seven participants (31.8%) were randomised to placebo, below the 3:2 methylphenidate:placebo ratio originally anticipated. This was due to one participant being randomised despite not being eligible, although this does not suggest failure of the randomisation sequence given the small number of participants randomised in total. This small number of participants allocated to placebo does make it difficult to draw accurate conclusions about the performance of this arm and increases the likelihood of spurious or misguiding results.
- Whilst no clear evidence of a selection bias appeared to exist, with no difference in baseline characteristics either between groups or relative to the larger cohort of patients with sarcoidosis who did not enter the study, the presence of "*demand characteristics"* (the risk of participants changing their behaviour in line with the study aims) leading to bias cannot be excluded. The large amount of interaction between the investigator and the

participants may have led to influence on the participants' perception of the study, such as all participants being aware that this research was forming a large portion of the investigator's thesis, which possibly led to participants filling the "good participant" role and striving to meet the study hypothesis (291). Alternatively, the process of participating in the research itself, including completing multiple questionnaires throughout the study may alter their thinking and perception, an effect that has been considered part of the "Hawthorne effect" and has been suggested should be broadened to "research participation effect" (292), leading to the unexpected performance of the placebo arm.

The *FaST-MP* study inclusion and exclusion criteria did not specify a minimum duration of disease, potentially leading to the inclusion of participants with a recent diagnosis who may have experience spontaneous resolution of disease (including symptoms of fatigue) during the trial. This issue was investigated through re-analysis of the collected data from *FaST*-MP. Excluding participants with a disease duration of less than 1, 2 or 3 years did not significantly alter performance of the active and placebo arms, although the number of eligible participants decreases accordingly. For illustration, the FAS scores for participants with a disease duration of at least 1, 2 or 3 years are shown in Figure 20. Despite the lower number of participants as the pre-study disease duration increases, the change in FAS scores over time, and the relative performance of the placebo and methylphenidate arms, remain unchanged from the scores seen without a pre-specified minimum disease duration at study entry.

Figure 20 *- Change in Fatigue Assessment Scale score (FAS) over duration of the study dependent upon duration of disease at study entry; (A) 1 year, (B) 2 years, (C) 3 years. Values are mean scores with 95% confidence intervals*



Number of participants per arm commencing study dependent on disease duration:
1 year: Methylphenidate – 11; Placebo – 6 (Total 17)
2 years: Methylphenidate – 10; Placebo – 5 (Total 15)
3 years: Methylphenidate – 9; Placebo – 4 (Total 13)

These factors are hypotheses for the relative performance of the methylphenidate and placebo arms, although the lack of clinical effect should not be considered a barrier to future trials investigating treatment for sarcoidosis-associated fatigue with methylphenidate. Any future study would require careful consideration of the inclusion criteria, the definition of the control arm to consider whether it would be representative of usual care, the optimal range of doses and the choice of outcome measures for defining clinical effect. An in-depth discussion of these issues is presented in chapter 8.

Strengths and limitations

The *FaST-MP* study had a number of strengths. It met its primary objective of determining the feasibility of undertaking a full study powered to confirm or refute the clinical efficacy of methylphenidate for sarcoidosis-associated fatigue. It provided estimates of recruitment rates and, through thorough screening of the entire cohort of patients with sarcoidosis under the care of the respiratory medicine department at the NNUH, also provided estimates of the proportion of patients with sarcoidosis who would be eligible for participation in any future study. In the process of recruiting participants, barriers to participation were also identified that could be modified to improve recruitment rates in any follow-up study from this. As the first parallel-arm study investigating methylphenidate in sarcoidosis-associated fatigue, it also identified the difficulty in maintaining blinding when utilising a cross-over study design and the resulting risk of introducing bias.

The study succeeded in identifying a number of issues with the study design that could be amended in future work, relating to the choice of inclusion criteria, randomisation sequence, duration of follow-up, choice of control arm or comparator, and choice of outcome measures. When considering outcome measures in a future study, the feasibility of using the activity monitors within this population was piloted successfully, suggesting they can be used in any future study. Finally, trial practices established with NCTU relating to risk assessment,

safety and quality management can be utilised as a basis for future studies expanding on the outcomes from *FaST-MP*.

The study also had a number of limitations. Participants recruited after December 1st had truncated follow-up, with the final five participants randomised in the study having follow-up truncated after 12 weeks receiving their allocated intervention. Only 16 participants had full data for the entire 24-week intervention period. This limits the assessment of outcomes after 12 weeks, including retention, adherence, tolerability of study medications, persistence of clinical effect, and exploratory analysis of clinical outcomes. This was also a single-centre study, which may make estimates of recruitment and retention optimistic when expanding across multiple sites as recruitment rates in single-centre studies are known to often be higher than across multi-centre trials (293). Finally, the clinical outcomes suggested no benefit from methylphenidate compared with placebo, which may relate to the lack of a true "usual care" arm in this study, stemming from the number of study visits and phone calls participants undertook. Therefore, the performance of methylphenidate relative to usual care alone remains unknown.

Considerations for a future study

Despite the lack of signal in support of methylphenidate use for sarcoidosis-associated fatigue compared with placebo, many factors support the feasibility of future studies into the use of methylphenidate or other neurostimulants for sarcoidosis-associated fatigue. Recruitment, whilst lower than anticipated, is likely to be sufficient for a trial powered for clinical efficacy performed across multiple sites with much larger populations of patients with sarcoidosis under their care, even allowing for lower recruitment rates than observed here. The use of activity levels recorded by wrist-worn monitors as an outcome measure also appears to be feasible based on the number of participants wearing the device for valid periods of time and the reliability of returning devices.

The included participants were able to have been diagnosed with sarcoidosis for any duration of time, although specifying a minimum duration of time since

diagnosis is likely to reduce the chance of spontaneous resolution of symptoms. Of the participants in this study, 17 (77.3%) had been diagnosed for at least one year, so specifying this as an inclusion criterion would still allow sufficient recruitment to occur whilst ensuring that the included population was less likely to see improvements in fatigue during the study which are unrelated to the intervention.

Although there was minimal difference between the methylphenidate and placebo arms, the data suggested that improvements occur quickly and persist across the study. Designing a study longer than 12-weeks for determining clinical efficacy of methylphenidate may be unnecessary based on these results. Of more importance is the choice of comparator. The exceptional performance of the placebo arm may have been due to the high level of clinical contact received by all participants. As a result, this study did not have a "usual care" arm. Ensuring the control arm is a true representation of usual care is more challenging. Reducing the number of follow-up visits may be beneficial, as well as feasible given that methylphenidate was well-tolerated. For this reason, a follow-up period of more than 12-weeks may be beneficial as it would allow a longer period without regular contact with the study team once dose titration had been achieved; for example, an 18-week study would allow the first 6 weeks to be used for dose adjustment with regular contact and review, followed by 12 weeks on a steady dose without regular contact. This would allow a closer representation of follow-up in an outpatient clinic and provide a more accurate control arm, but would also require participants to be confident in being able to contact the study team if any issues were to occur and a robust pathway in place for dealing with issues as they arise.

A final consideration reflects the reduced anxiety and perceived physical symptoms identified in the placebo group which may have led to the reduced fatigue scores seen within these participants. Whilst it is important to consider the small number of participants allocated to receive placebo, and the potential impact upon the results seen in this group, it is also important to consider how the improvements seen in fatigue may relate to the reduction in other symptoms. Avoiding the need to employ medication for management of chronic fatigue would be beneficial; given the improvements seen in the placebo group and the known influence of anxiety on

fatigue (289), including a psychological intervention prior to enrolment should be considered for any future trial. This addition could screen out patients who would benefit from such an intervention, leaving only participants more likely to benefit from a pharmacological intervention directly targeting fatigue, although it would increase the cost of any such trial.

None of the issues raised would be insurmountable for designing and implementing a future study investigating the clinical efficacy of neurostimulants for the treatment of sarcoidosis-associated fatigue; the proposed design changes would ensure that only patients likely to require and benefit from methylphenidate would be included.

5.4 Conclusions

The results from the quantitative data collected during the *FaST-MP* study has demonstrated the feasibility of performing future trials investigating the clinical efficacy of neurostimulants for the treatment of sarcoidosis-associated fatigue, as well as identifying the issues that may influence the clinical outcomes in the placebo arm. Recruitment, retention, safety and adherence outcomes supported the feasibility of future trials. Outcomes in the placebo group raised concerns about what should form the control group as the placebo group within this study did not reflect what would be considered “usual care” in an outpatient setting. The lessons learnt can help to influence future trial design to account for these issues.

In the next chapter the outcomes from the focus groups, undertaken as part of the *FaST-MP* study to investigate individual experiences of trial participation, are presented. The qualitative method allows a closer inspection of the impact of sarcoidosis-associated fatigue to individuals, as well as the improvement experienced during the study. Additionally, changes to trial design and methods are discussed with participants, utilising their experience of the *FaST-MP* trial to generate ideas that would improve future work arising from this feasibility study.

Chapter 6: *Participant perceptions of the FaST-MP study – outcomes from focus group discussions*

Research Ethics Committee (REC) Approval Gained as part of the *FaST-MP study*
REC reference – 16/EE/0087

6.1 Introduction

In chapter 4, the *FaST-MP* study provided important data regarding the feasibility of designing, implementing and undertaking a phase III study investigating interventions for sarcoidosis-associated fatigue. The results suggested that undertaking a randomised-controlled trial in patients with sarcoidosis-associated fatigue was feasible, although exploratory clinical outcomes suggested improvement in fatigue scores compared with the placebo arm . In this chapter, the results of focus group discussions with *FaST-MP* participants, undertaken alongside the study prior to unblinding of allocation, helps to bring into focus the positive and negative aspects of trial participation, particularly relating to receiving methylphenidate, as well as suggesting practical changes for any future study investigating the clinical efficacy of neurostimulants.

Background

Although relatively uncommon, the use of qualitative methods alongside randomised controlled trials offers many benefits, including developing and refining interventions or outcome measures, as well as exploring the outcomes from the study and the reasons for them (294). Previous trials have used a mixture of RCTs and qualitative methodology to aid a number of outcomes. This includes better understanding around how trials work in the real-world, drawing attention to outcomes that are important to participants, and understanding simple interventions where complexities beyond the intervention may exist (295). There are specific examples of how qualitative work has been highly beneficial in previous RCTs; in one case qualitative interviews explored issues and identified changes relating to recruitment, leading to significant improvements in recruitment (296). In another example, interpretation of previous negative results enabled further insight into the effect of intervention that was not identified from quantitative work (297).

As part of the *FaST-MP* study, qualitative data collection was planned to enable participants within the study to have a direct impact on the design of any follow-on study investigating clinical efficacy. This would maximise the chances of optimal

recruitment and retention, as well as influence the selection of outcome measures to ensure that they are relevant to patients. This methodology ensures that participant experience and opinions directly influence future trial design.

In addition to eliciting opinions about the trial design and methodology from those who had participated in the study, the qualitative methodology allowed the possibility to explore the effect of the intervention on participants within the study. Exploring the positive or negative aspects of the intervention itself, and the effect experienced by participants, gives meaning to the changes in fatigue score seen. It can illuminate examples of changes seen by individuals during the study period which may provide a different picture to that seen in the quantitative data. The complexity and multi-dimensional nature of fatigue makes a convergent mixed methods approach, combining the logical empiricism of quantitative methods and the constructivism of qualitative methods, an attractive way of exploring the impact of the study on participants. This methodology has been explored before and provides additional benefit over a solely quantitative approach (298). The quantitative outcomes were reported in the previous chapter; in this chapter the focus group outcomes, relating to the effect of fatigue, the impact of alleviating fatigue through intervention and suggested changes to related future studies, are reported.

Objectives

The focus groups were performed with the following objectives:

1. Description of participant experience of receiving medications during the study, including the effect on their lives and changes from pre-trial experience of fatigue. As part of this objective, pre-trial fatigue was discussed by participants.
2. Explore positive and negative aspects of participation within the FaST-MP study, including possible improvements or changes for any follow-on study from FaST-MP which may improve participant recruitment, retention or experience within that study.

6.2 Methods

In order to explore participant perception of the FaST-MP study, three focus groups were organised to allow extended discussion with participants of the study. All participants of the FaST-MP study were offered the chance to attend one of the focus-groups; the participants within the focus groups represented a convenience sample of those who were able to attend any of the three focus group sessions.

Focus groups were chosen as the preferred methodology for exploring participant experience of the FaST-MP study because the group discussion was felt to allow interaction between participants, inviting them to discuss their own experiences and reflect upon or consider other viewpoints. The focus group methodology was also felt to be more likely to generate new ideas relating to future clinical trials as the facilitated discussion allows participants to "piggyback" on each other's ideas; this positive aspect of the focus group format makes it ideal for idea generation and project evaluation (299). Homogeneity in the composition of focus groups is considered important to encourage free-flowing dialogue between members of the group (300). All members of the focus groups were patients with sarcoidosis and had recently completed the FaST-MP study; this was felt to represent two shared experiences that would facilitate discussion between members of the group through a "common ground", increasing the likelihood that focus group members would consider themselves equal. In this respect the group could be considered homogenous due to this shared experience despite heterogeneity in social background and demographics. In addition, the methodology represented the best opportunity of maximising the amount of data collected in an appropriate time scale.

Three audio-recorded, moderated focus groups were planned for participants of the FaST-MP study who had completed their participation in the FaST-MP trial (i.e. had completed their week 30 assessments). Each focus-group was planned to have between four and six participants, dependent upon participant availability. Focus groups with less than four members were not permitted. All focus groups were undertaken at the same location (the Bob Champion Research and Education Building at the University of East Anglia, Norwich). A pre-specified topic guide was

used to facilitate discussion using open-ended questions (topic guide available within appendix 4). The two key topics included were participant experience of trial participation (both positive and negative) and suggested changes to the study which might improve the future recruitment or retention of participants to any follow-up study to FaST-MP. Each topic heading included a series of open-ended questions, some containing prompts to aid discussion if required. To avoid embarrassment or discussion of sensitive issues relating to impact of fatigue, questions pertaining to the impact of fatigue were not included in the topic guide and were not asked during the focus groups. Where participants began to discuss the impact of sarcoidosis-associated fatigue on their lives during the course of discussion within the focus groups, these conversations were allowed to continue and were permitted as long as participants were comfortable continuing the discussion. No additional questions exploring the impact of sarcoidosis-associated fatigue were asked by the moderator (Dr C Atkins) during these discussions.

All participants within the focus group provided written informed consent as part of the consent process for the FaST-MP study; this was not a mandatory aspect of the FaST-MP study and only those providing written consent were approached about participation within the focus groups.

Audio data collected from the focus-groups was transcribed, with transcription and participant identity within the transcripts checked and confirmed by the lead researcher, Dr Chris Atkins. The audio data was complemented by written notes collected by Dr Atkins, with a research assistant present during each focus group to assist with the running of the session. Analysis of the data was undertaken using a thematic analysis approach, according to recommendations by Braun and Clarke (301). This involved the following steps:

1. Familiarisation with the data
2. Generating initial codes
3. Searching for themes
4. Reviewing themes
5. Defining and naming themes
6. Report production

Dr Chris Atkins undertook data familiarisation, code generation and identification of initial themes. These initial themes were then modified through back-and-forth discussions between Dr Atkins and Dr Andrea Stockl, who was the supervisor for the qualitative aspect of this project. Coding of themes was assisted by NVIVO 11 software.

6.3 Results

Fourteen participants from the FaST-MP study took part in the three focus groups that were undertaken, representing 63.6% of the total number of participants within the FaST-MP study. Each focus group took between 75 and 120 minutes in total. The age, gender and allocation to treatment or placebo arm within the FaST-MP study are shown in Table 46 below. All the focus groups took place before unblinding the FaST-MP study, therefore none of the participants were aware of their treatment allocation at the time of the focus groups.

***Table 45** - Focus group participant demographics*

Focus group number	**FaST-MP Trial ID Number**	**Age**	**Gender**	**Baseline Fatigue Score *(FAS)***	**Allocation arm in *FaST-MP***
1	002	59	F	34	Methylphenidate
	003	71	M	23	Methylphenidate
	005	53	F	30	Placebo
	006	56	M	26	Methylphenidate
2	001	69	F	26	Methylphenidate
	004	59	M	28	Placebo
	007	44	F	42	Placebo
	008	53	M	38	Methylphenidate
	009	52	M	22	Methylphenidate
3	011	65	M	40	Placebo
	013	65	F	45	Methylphenidate
	014	67	F	35	Placebo
	016	34	M	44	Methylphenidate
	019	69	M	31	Methylphenidate

Three main themes arose from the focus group discussions. These can broadly be broken down into problems experienced through each patient's sarcoidosis and associated fatigue prior to trial participation *("Before")*, the experience of trial participation and the effect of medications experienced by participants *("During")*, and factors that could be changed for any follow-on study *("After")*.

Before - Biographical disruption, premature aging and the invisible illness

The concept of biographical disruption was first described by Michael Bury in 1982 and relates to the disruption to an individual's life in multiple ways, having significant impact upon the concept of self and future self. Bury described chronic illness as "that kind of experience where the structures of everyday life and the forms of knowledge which underpin them are disrupted" (302). Biographical disruption has never been explored in patients with sarcoidosis though it has been identified in other chronic diseases, including patients with chronic fatigue syndrome (303). Given the chronic nature of sarcoidosis and the interaction between symptoms and quality of life, it is unsurprising that this framework was found to have applications to the cohort of patients included here. For the patients with sarcoidosis here, there was significant variation in the level of disruption encountered, but those who suffered severe fatigue described a life-altering change in their own capabilities:

"Once I had developed severe chronic fatigue it was like the end of my life, and I was so restricted in what I could do, and even going to the supermarket is a major chore for me". (013, Focus group 3)

The description of the impact as the end of a life reinforces the potential impact that fatigue can have on normal activities, and the ending of what is considered a normal life. The concept of "brain fog" as a major aspect of the fatigue was raised by two participants, with one discontinuing driving because of this aspect of her fatigue. Others described having a "day-to-day fight" with fatigue, dreading waking up in the morning because of their fear of facing the day and the tasks it entails. As noted in Bury's work with rheumatoid arthritis patients, adaptations were

undertaken by participants to deal with their symptoms and their disability. For one participant, this meant a very prescribed set of activities to work within his capabilities:

"If I'm going outside I'm going to do everything I need to do outside in one go, rather than backwards and forwards, backwards and forwards… I had to write down a list of what I needed to do today, what's the best way to do it, and plan days out". (016, Focus group 3)

In this case, function was maintained through planning and the need to get things done. This participant had children at home which meant that he had to work around his limitations from fatigue, explaining that it he "didn't get to stop" as a result of needing to be active for his children. Other participants, whilst using similar techniques of pacing activities, coped by withdrawing from social situations when she felt particularly bad:

"My friends say, "Do you want to come out for a meal, Monday night?" I'll say, "Can't do it." I can only pick one thing in a day to do, I can't rush home, get ready, and go out and do something else. It just doesn't work." (014, Focus group 3)

For some of the participants, the impact of fatigue and sarcoidosis on their normal function had led to a perception of being prematurely aged, restricted in function and quality of life compared with peers of similar age and lifestyle. Relating to the impact of fatigue on lifestyle, one participant mused about "how much [he] had missed out on in life" (009, Focus group 2). Frustration was expressed about life lost because of the symptom, including one participant who felt that he was suffering the effects of aging at an earlier age than he expected:

"I know we all get old and slow down and fall apart and whatever, but it's all happening too early in life. I have people around me the same age and they're still living an active life and me, I'm not, even though… not as much as I should do." (009, Focus group 2)

Another participant considered whether it was her expectations of the aging process that were wrong and that she was blaming the sarcoidosis for symptoms

that were related to her age, although this may have been an attempt to "normalise" her symptoms; she had previously appeared shocked and irked when her son had suggested that 59 years of age represented "getting old". Six of the participants expressed frustration relating to this feeling of premature aging. This concept, when considered alongside the changes that were made to lifestyle to maintain function, bear parallels to the concept of "selective optimisation with compensation" as part of a successful aging process (304). The restriction of activities mirrors the domain of selection, concentrating on high priority domains such as work and looking after other members of the family. The optimisation domain, moving towards tasks that "enrich and augment," does not initially appear to be fulfilled here. However, the optimisation strategies appear to surround necessary tasks, relating to work or carer responsibility for younger members of the family, at the cost of other activities; for example, this meant falling asleep early in the evening for one participant and missing out on time with his partner. Finally, compensation is attempted with strategies that will maximise functioning for individuals. These strategies include pacing, structuring and limitation of tasks, as shown above, to maximise achievement within an individual's capabilities. Participants had tried different treatments, remedies and managements for fatigue, without improvement. Even attempts at restoring energy through sleep failed to achieve the desired effect:

"I know however tired I am I won't go off [to sleep]. I have laid down before and thought, "Well I'll try and have a sleep in the afternoon and see if that gets me feeling better tomorrow," but that doesn't because I don't go to sleep. I can't" (002, Focus group 1)

The result of these actions appears to be a similar strategy to those manging the aging process later in life, but one which can never be fully achieved due to existing requirements on their time such as work or families.

Returning to Bury's concept of biographical disruption in chronic illness, this has been successfully applied to patients with many different chronic diseases, including those with potentially clear physical or functional impediment (e.g. rheumatoid arthritis (302) or stroke (305)) or with clearly understood implications

for third parties (e.g. cancer (306)). In contrast to these examples, in sarcoidosis the manifestations of the disease were not felt to be immediately obvious, including the symptom of fatigue. Participants raised examples of the condition being invisible to other people. Examples were cited of both medical professionals, such as primary care physicians having little familiarity with sarcoidosis and its potential manifestations due to the relative rarity of the disease, and lay people being unaware of the condition. In the case of the latter, the invisibility related to the lack of physical symptoms relating to the condition, with one participant describing his sarcoidosis as "one of those hidden diseases" (006, Focus group 1). Another participant felt that the invisibility was particularly difficult when dealing with work and employers:

"If you try and explain it, especially at work, it's really hard to explain, because you don't look ill, but you are ill, and they don't understand". (005, Focus group 1)

This participant worked in a customer-facing role at a high-street shop, continuing to work despite significant fatigue, but when her disease flared it was difficult to explain how it was affecting her to her employers. This invisibility, and resultant difficulty in others understanding the illness, leads to difficulty in patients feeling able to access the classic sick-role behaviour that was suggested by Bury's biographical disruption. Instead, the lack of a visible or well-understood medical condition removed acknowledgement from others. A similar framework was identified by Sarah Nettleton in patients with medically unexplained symptoms, including fatigue, where "permission to be ill" was not granted due to a lack of diagnosis (307); in the case of patients with sarcoidosis and associated fatigue, the lack of visible and understandable illness appeared to cause comparable issues.

Prior to commencing medications within the study, it was clear from discussions that the sarcoidosis-related chronic fatigue suffered by all the participants had significant impacts upon their life beyond just reduced function. The feeling of a life being "over", or reflection on years of life not fully lived, paint a vivid picture of the negative impact that fatigue has upon quality of life.

During – Effect of Medications and moral ambivalence on their use

The patients in this study had suffered the chronic effects of sarcoidosis; their descriptions of the impact of the fatigue related to the condition upon their lives appeared to comply with the framework of biographical disruption. Within the *FaST-MP* study, an opportunity was afforded to receive medications that could ameliorate or even fully reverse this symptom. When asked about their rationale for participating in the study, four participants discussed the altruistic aspects, wanting to "put something back in" or help others and another two participants spoke about the reassurance from receiving the additional tests performed during the study. However, one primary driver was the hope of receiving the active medication and the direct benefit that may come from this.

For those who perceived benefit from the medications, the positive impact upon their life was remarkable. Participants who had spoken of lost life and poor function relative to their peers, discussed in the previous section, noticed marked improvements in their quality of life. For one patient who had severe fatigue, the effects of the medication had a significant benefit:

"I felt like I was whole again. I still didn't have the same normal energy levels like I had before I became sarcoid, but at least I could get on with my life and not feel like my life was diminished to the extent that I was no longer really functional." (013, Focus group 3)

This participant continued to run a business and was involved in dog breeding; having previously shown dogs at competitions her fatigue had left her unable to do this. During the course of the trial she felt was able to return to showing her dogs at competition again due to her improved energy levels.

Such improvements in function were not uncommon, with nine of the participants in the focus groups reporting improvements. For one patient, commencing medications led to a marked improvement in her "brain fog", describing the feeling as if "this cloud had lifted" (002, Focus group 1). Another reported improvement at work, improvements in willpower and drive, and accomplishing tasks that he had been planning for months but felt unable to do. These were a few specific

examples, but a general theme from these patients was the restoration of some semblance of a normal life, one participant stating that he "felt alive for the first time in years" (009, Focus group 2).

As described quantitatively in the previous chapter, significant benefits were perceived by participants receiving the placebo. At the time of the focus groups none of the participants were unblinded, therefore the reasons for this improvement could not be explored. The magnitude of effect is illustrated by one participant who noticed significant life changes during the study despite not receiving the active medication:

"Huge differences. We've been able to lead what I would say is a more normal life after not managing much at all, being able to keep up with my 11-year old, almost. Being able to have a social life, not fall asleep during the day, not fall asleep on the sofa every time I sat down."

"It makes life – for me it made life easier, it wasn't that constant, "Oh God I can't do this." … For years – that's the first time in a long time I wanted to get up each day and felt alive to get up each day and managed to enjoy going for a walk." (Both 007, Focus group 2)

Other examples of improvements were given by participants who had received placebo; in one case a participant who had given up driving due to "brain fog" felt well enough to restart driving her car during the study despite not being allocated to the methylphenidate arm.

Relating this re-gain of function and quality of life does not easily fit with previous concepts of chronic illness; participants did not notice any difficulty in returning to normal function and were grateful for the opportunity to experience this, even for the short duration of the study. This in itself presented a potential problem as ongoing treatment was not available at the end of the study. As one participant rationalised:

"A lot of us have done this knowing it's not available but we're all, in the back of our heads, have got that it's one step closer to it potentially being available. Where

we're not going to have to jump through hoops and do all this to get hold of it". (016, Focus group 3)

For this participant, even knowing that the duration of medications was finite was acceptable in the bigger picture of making this treatment more widely available, returning to the theme of altruism as a reason for participation knowing that any improvement during the study was likely to be transient.

Despite the dramatic improvements there were some concerns over the ongoing use of methylphenidate that were discussed within the second focus group. One participant within the group considered how the use of medications to feel better within this group could lead to potential drug-seeking behaviour. During the study he had noticed benefits to his normal fatigue levels but had also noticed that the effect was not the same over time:

"That's what my worry was, I felt my body got used to it." He went on to say, *"It's almost as though you got used to the smaller dose and then start to take the higher dose, bang, I got that hit again."* (008, Focus group 2)

The use of language associated with illicit drugs was echoed by other participants, in other focus groups as well, referring to getting a "hit" or a "buzz", as well as "coming down again" as the medication wore off. This moral ambivalence of using the medication was difficult to resolve and there was a clear concern that long-term use of the medication might result in individuals "chasing" a hit and leading to medication abuse and addiction. The main rationale for this concern related back to the marked positive effects that these individuals had felt. The same participant who had initially raised these concerns expressed it as such:

"The only problem with that is four of us sat around the table and said we felt great. I think it would just become – who doesn't want to feel great all the time?" (008, Focus group 2)

Whilst this is a valid concern, it is interesting to note that the participants all agreed that they felt great – even though their level of function and energy had "just been normal, how it should be really" (009, Focus group 2). Simultaneously, whilst

medications had restored them to what was considered a normal quality of life for their age, it appeared they had previously created a "new" normality to enable them to live with their fatigue. This concept of patients creating a "new normal" as a form of coping strategy has been described before in other conditions including traumatic brain injury (308), inflammatory bowel disease (309) and cancer (310). The impact of returning to pre-morbid levels of function in other conditions, or in sarcoidosis, has not been explored. For some of the participants here, returning from their created "new normal" to the level of function they would expect to be able to do when well ("true normal") led to difficulties adjusting, mistaking their "true normal" level of function for a synthetic or artificial "high". This in turn had led to this ambivalence on using medications to improve function so markedly.

Despite these concerns, participants were keen to continue with the medication. Those participating in focus group 2 wanted to ensure that the medications were controlled and used at as low a dose as possible, but this negative aspect of receiving methylphenidate or related medications was not raised in either of the other two focus groups. No other significant issues were raised relating to adverse or negative effects of methylphenidate. The overwhelming outcome from those who received benefit was that the medications enabled a return to normal life and a significant improvement in quality of life as a result.

After – Feedback on study design and outcome measures

Beyond the potential negative connotations and moral ambivalence of receiving stimulant medications for sarcoidosis-associated fatigue, specific negative aspects of the *FaST-MP* study design were raised by participants. One major problem related to a key aspect of the study, notably the questionnaires used for clinical outcome measures. For some of the participants, frustration was expressed at the number of questionnaires and the overlap between them. Although part of this was frustration at the time it took, in some cases the symptoms of fatigue led to actual difficulty in completing the questionnaire pack, one participant recalled thinking "Gosh, how am I going to get through this [questionnaire pack]?" (013, Focus group

3) once she had discontinued the medications. Five of the participants felt that too many questionnaires were included, although two participants were happy with the number of questionnaires used if it meant that the study was not compromised for outcomes.

Whilst the number of questionnaires was considered a problem, a bigger issue was raised concerning the sensitivity of the questionnaires for collecting data which reflects improvements for the patients. The questionnaires were described as "not relevant," or "too vague" to adequately pick up the impact of fatigue on daily life; this lack of relevance was echoed by others, especially relating to the variability of fatigue day-to-day and the difficulty in giving an answer reflecting the severity of fatigue over a period of several weeks:

"I think the answers were very vague as well, especially the multiple-choice ones where it's 'sometimes' or 'often'. Well, and then it's over the last two weeks. Well, actually, I've had some good days and I've had some bad days but I can't write, "Well, actually, some of it was this, but some of it was this," or, like you said, it's often or sometimes." (016, Focus group 3)

An initial concern when designing the trial was that questionnaires were being administered too frequently, as often as every two weeks during the first six weeks of the study, but the feedback from focus group participants was that the visit schedule was not too onerous and yet the ability to track fatigue levels and the effect of medications was still hindered by not being able to measure fatigue levels frequently enough to obtain the resolution of data to adequately show change in fatigue. Clearly seeing or contacting a patient on a daily basis to score their fatigue levels is likely to be impractical and, for the participants, potentially tiresome, although a self-report diary may enable collection of this data. Participant 16, who had identified the vagueness in our method of measuring and tracking fatigue, offered a suggestion:

"I think, almost, like a daily diary. Not like a full questionnaire every day, but even if it's just notes for us. Some way of logging, "Today was a rubbish day, it took me almost two hours to get out of bed and I went back to bed because I was just too

tired," and other days, "I got up, actually, I was really good until lunch time." (016, Focus group 3)

Whilst this form of data would allow greater insight into the impact of fatigue, it may present difficulties in quantitative analysis to detect change over time or change between groups unless self-rating scales were included to score daily fatigue levels. The use of technology was suggested, using a smartphone-type device as a way of administering a simple likert or visual analogue scale question on a daily basis relating to fatigue, with the option to add additional data as a diary entry if needed. This was considered interesting by the members of focus group 3, where this discussion had occurred, and offered a solution to what was considered a significant problem with the chosen outcome measures.

Another outcome measure being evaluated in the *FaST-MP* study was the use of activity monitors, worn for three seven-day periods during the study. The output from the devices, as shown in the previous chapter, suggested that it was possible to reliably obtain valid data from them. The GENEActiv activity monitor had previously been piloted and preferred to a competing device, as described in chapter 3, but the experience of using them within the *FaST-MP* study split opinion. Three participants found no problem in using the devices and spoke about the devices positively, putting it on and forgetting about it. However, four participants spoke negatively about the GENEActiv device, describing it as "too big", "inappropriate for work", "uncomfortable", or generally finding the rubber strap uncomfortable. Mention was also made of the lack of watch face (also mentioned in the feedback on the devices from the pilot study reported in chapter 3) and unpleasant appearance; suggestions were made for the use of commercial devices, notably Fitbits, which one of the participants wore normally, or apple watches. These had the benefit of being more functional and more pleasant in appearance.

Finally, criticism was also aimed at the facilities used for the modified shuttle walk tests. These occurred in the clinical trials unit within the Norfolk and Norwich University Hospital, itself a repurposed formed ward area. Whilst there was space for the necessary track, in practice it was surrounded by potential obstacles and could be crossed by members of staff within the unit accessing storage areas.

Incidents had occurred where collisions or interrupted tests had resulted from other staff members walking onto the track by accident. A number of participants raised this during discussions:

"…when you do that [walking test], that needs a more defined area. Doing it in the corner of a corridor with filing cabinets, desks, chairs…" (006, Focus group 1)

"It wasn't very good when I knocked that person walking was it?" (003, Focus group 1)

"I had a nurse come in at the last, she stopped me and I was in the peak wasn't I? The peak of my physical fitness and she came across." (002, Focus group 1)

"[It's] just embarrassing when you're walking down the corridor and someone comes around the corner." (008, Focus group 2)

The majority of complaints came from members of focus group 1, which relates to problems with staff awareness early in the trial. This appeared to become less frequent as the trial progressed and staff in the unit were more aware of the test being conducted. Participants expressed frustration at these incidents occurring, reflecting the importance of obtaining the best possible result in their walking test for them and the failure to do this when they were interrupted, or embarrassment at running into a member of hospital staff. For some it was a humorous event which they laughed at when recollecting the event, but it was universally agreed that the location was not ideal for a modified shuttle walk test. One participant in focus group 3 went on to suggest a static test, considering a treadmill-based test to be preferable given the lack of space for a shuttle walk test to occur whilst simultaneously allowing for incremental effort through faster speeds or increased inclines. This was also raised by another participant in another focus group who had noted that his exercise performance on the flat was good and may not reflect his true limitation:

"I mean, I done quite well with the walking test on the flat, but I think steps [stairs] or something of that nature would give a bigger indication of how I struggle in my day to day." (008, Focus group 2)

An ergometer, be it treadmill or cycle-based, would have overcome these shortcomings and was suggested by one focus group member as an alternative, and was considered preferable to the MSWT used in the FaST-MP study.

6.4 Discussion

This chapter reports an analysis of how participants within the *FaST-MP* study found involvement in the trial, both positive and negative, as well as the problems they faced before receiving the trial intervention relating to the impact of fatigue on their daily lives. The findings identified here overlap with previous data from chronically fatigued patients with rheumatoid arthritis (RA), another chronic condition. The patients with RA described an unpredictable or variable fatigue, a significant effect on everyday life, and the emergence of self-management strategies to minimise the impact of fatigue to the individual (311). In the patients with sarcoidosis included here, daily variability in fatigue was mentioned relating to difficulties in measuring the symptom in a relevant way within the study. The impact of fatigue upon day-to-day life prior to the study was clearly illustrated by examples, with self-management and pacing techniques employed by some participants to enable essential daily activities to occur. The characteristics of the fatigue described appears to be similar to those described in other conditions. The resulting impact of this sarcoidosis-associated fatigue leads to disruption of an individual's life, in keeping with Michael Bury's thematic framework of biographical disruption which was described above (302). This is the first time that patients with sarcoidosis have been investigated in this way, and the results are in keeping with results from other chronic diseases.

It was notable that the presence of fatigue and reduced energy levels led to some of the participants feeling prematurely old, and the coping strategies employed by them to maintain function is in line with those employed as part of "healthy aging," maintaining function with a focus on critical tasks such as work or caring for family members (304). The insight from this could be used to enable patients who wish to manage fatigue, rather than seek pharmacological treatment with agents such as

methylphenidate, to follow pacing techniques which require restriction of activities to optimise others. This is particularly important when considering the somewhat unexpected quantitative results from the *FaST-MP* study relating to the relative efficacy of methylphenidate compared with placebo; despite appearing safe and well tolerated, exploring other options before considering neurostimulant therapy appears particularly relevant as significant improvements in fatigue, with discernible improvements cited in examples from participants included in the focus groups, were seen in focus group participants who had been allocated to the placebo arm within the *FaST-MP* study.

It was unexpected, therefore, to see the ambiguity in discussions from some participants relating to taking the medications and returning to a "normal" life, for many an incredible and previously unreachable achievement. The inability to split apart the notion of a prescribed medication to return to normal function from that of an illicit substance used to chase an artificial high was an unexpected finding, indicating a reticence on the part of some participants to expose themselves to the possibility of addiction. This reinforces the importance of treatment strategies involving symptomatic treatment of fatigue with neurostimulants to be undertaken with strict oversight and monitoring by secondary care, ideally with experience of using these agents. Joint goal setting by patients and clinicians, as well as selection of patients to reduce the risk of abuse, is also important. These points were considered very important by one participant to prevent him, and others, becoming dependent upon a medication and self-medicating with ever-higher doses.

During discussion of the potential changes that could be made to any related future studies a number of positive suggestions were made. The importance of ensuring an appropriate facility for conducting all outcome measures, specifically exercise-based ones such as the modified shuttle walk test, was reinforced through discussions with participants. Suggestions included:

- Future measures of exercise capacity should be considered in light of the expected localities where trial activities would expect to be taken place.

- The use of static equipment such as exercise bikes or treadmills may provide a reasonable alternative as many hospitals have access to a physiology laboratory for cardiopulmonary exercise testing, which could be utilised for this purpose.

The other major changes suggested related to the questionnaires and the activity monitors. Problems with both of them, notably the inability of the questionnaires to measure daily fluctuations in fatigue and the discomfort of wearing the activity monitors, led to the suggestion of a unified solution in the form of smart phones or smart watches – these devices would have a number of advantages:

- They are able to track activity levels as part of in-built health data collection
- They would be able to administer a simple questionnaire on a daily basis (e.g. rating fatigue level between 0-100), tracking daily fatigue levels.
- Different types of wrist straps are available for most smart watches, which would provide participants with the option to choose a strap that would be most comfortable for them.

Using the example of the apple watch, specific developer tools are available for health research; development of a program ('app') to collect both activity and fatigue data was considered an interesting solution by some participants and could be considered as a way of collecting the necessary resolution of data for any future study.

There were limitations to these focus groups. Three focus groups were convened, allowing 14 of the 22 *FaST-MP* participants to discuss their views. However, new ideas and discussions were still being raised in the third focus group, suggesting that saturation was not reached within the three groups. There was also limited scope to explore in depth the impact of fatigue on daily living which, though not the primary rationale for undertaking focus group discussions, would have provided interesting data in a disease group that has not previously been investigated using these methods. Focus groups were not the ideal forum for discussing this in depth and contributed to the decision not to explore the impact of fatigue on individual patients prior to study entry. Future work would require semi-structured interviews

with individuals to validate the findings relating to impact of fatigue on these patients. Finally, the focus groups occurred whilst *FaST*-MP was ongoing; as a result, participants were still blinded to their allocation at the time of the focus groups, so no insight could be gained into why participants believed such a significant benefit was possible on the placebo medication, or their reaction to finding out their allocation. Given the aims of the focus groups it was felt appropriate to explore these issues before unblinding, reducing the length of time between completion of the main study and participation in the focus groups and hopefully aiding recall of any issues that occurred during the study. Despite these limitations, the data collected here provided clear examples of benefit from neurostimulant therapy to individual patients, as well as identifying weaknesses of the *FaST-MP*'s trial design and suggested potential changes for any follow-up study.

6.5 Conclusions

This chapter has given insight into the problems faced by patients with sarcoidosis-associated fatigue, the potential benefits of neurostimulant therapy to an individual through some illuminative examples of return to function and improvement to quality of life, as well as potential suggestions for alterations to any successor to the *FaST-MP* study. Measuring quality of life in any future study investigating treatment for sarcoidosis-associated fatigue is clearly an important outcome. In the next chapter, two methods of measuring health-related quality of life are compared to identify the preferred instrument for any future study.

Chapter 7: *A Comparison of Measurements of Health-related Quality of Life in patients with Sarcoidosis*

Research Ethics Committee (REC) Approval Gained
REC reference – 17/LO/1872

7.1 Introduction

The results of the *Fatigue and Sarcoidosis – Treatment with Methylphenidate (FaST-MP)* feasibility study have shown that it is feasible to perform trials into the use of neurostimulants for treating sarcoidosis-associated fatigue. Whilst recruitment to the study was acceptable, and retention of participants through the study was excellent, negative issues were flagged by participants during focus group sessions relating to the outcome measures used. In the focus group discussions, a number of participants suggested that it would be beneficial to reduce the number of questionnaires in any future study, and to ensure any future questionnaires were able to reflect changes in how participants felt whilst receiving medications.

One outcome from the exploratory analysis of the questionnaire data collected in *FaST-MP* was the difference seen between the two health utility scores at baseline, derived from the EQ5D and SF-6D questionnaires. In order to better understand this an additional project was undertaken, administering both the EQ5D and SF-6D (through the longer SF-36) simultaneously, alongside other instruments relating to fatigue, anxiety, depression and disease status. Some of these factors were seen to vary over the course of the study between the methylphenidate and placebo arms, therefore the influence of these upon the EQ5D and SF36 utility values is of interest.

Determining which of the EQ5D and SF-6D instruments are preferable for measuring health utility in patients with sarcoidosis is important for any future health utility analysis, as well as minimising questionnaire burden for participants in future trials. This study was undertaken to understand what causes the relative difference in performance of the EQ5D and SF-6D questionnaires by collecting and analysing cross-sectional data from a cohort of patients with sarcoidosis.

Background

Quality of life is an important consideration in sarcoidosis, either through the direct effects of granulomatous inflammation from the disease (312), constitutional

symptoms including fatigue (122, 313), or side effects of treatment which can cause symptoms of its own (314). These factors are discussed in depth within chapter one of this thesis.

Health-related quality of life (HRQoL) is distinct from quality of life, although distinguishing between the terms can be difficult. Quality of life is a concept which encompasses all aspects of life and is difficult to measure, requiring psychological, social and economic wellbeing to be considered alongside direct health-related effects of both disease and treatment. The term "Quality of Life" in medical literature does not have a defined meaning and is frequently substituted for HRQoL (186). By contrast, HRQoL is more narrowly-defined, as it focuses on the health or disease status of an individual and how this influences quality of life. HRQoL itself can be defined in multiple ways, including the frequently used term "health state" (187).

To facilitate comparisons of interventions, "quality-adjusted life years" (QALYs) are typically used to measure the impact of treatment on length and/or quality of life. The National Institute for Health and Care Excellence (NICE) requires the use of QALYs when appraising health technologies (315). In order to generate QALYs, weighting of preferences for health states is required. This is termed *health utility*, with more desirable health states having a greater weight. Utility is scored between 0 and 1; 0 indicates death and 1 indicates full health, with negative health states indicating a health state considered worse than death also permitted (316). QALYs are calculated from both HRQoL and survival; an individual in a health state associated with a utility value of 1.0 living for five years would generate five QALYs, as would an individual living in a health state of 0.5 for ten years, although this does not consider discounting of future QALYs which reduces the number of future QALYs as survival increases. NICE currently recommends a discount of future QALYs at a rate of 3.5% per year but can vary this amount (317). QALYs consider both survival and changes in health states, combining both these markers into a single universal index which enables comparison across different areas of healthcare. The number of QALYs lost or gained across a population during an intervention forms

the basis of *cost-utility analysis* (316), which can influence decision-making on resource allocation.

In order to calculate QALYs it is necessary to calculate HRQoL and health utility. Patients can be asked to rate their own health-related quality of life using measures such as the EQ-VAS on a scale of 0-100. Although there are drawbacks to this method, specifically the end-of-scale bias leading to respondents being less likely to use the extreme ends of the scale, it is a simple way of measuring health status and it directly records an individual's perception of their own HRQoL (316, 318). It is also not a true measure of health utility as it does not require the subject to consider sacrificing time or health, or indeed express a preference for their current health compared with other possible health states. Alternatively, questionnaires can be used to indirectly measure health state values. These instruments, which include the EuroQoL-5D-5L (EQ5D) or the Short Form 6-dimension (SF-6D, which is derived from SF-36 values (319)), have multiple dimensions relating to health; the responses across all the dimensions within the instrument can be converted into a health state. Previous work in healthy populations allows these health states to be converted to a utility value, with different methods used for determining preference of health states. The two main approaches are the standard gamble (SG) and time trade off (TTO). The SG approach, which invites patients to consider gaining perfect health (health utility value = 1) compared to their current health, at a risk of suffering the worst possible outcome (health utility value = 0). The SG approach was used to calculate a value set for the SF-6D instrument (319). This method is liable to loss aversion and probability weighting biases leading to higher utility vales being reported than with the TTO method (320). By comparison, the TTO approach invites patients to consider how much of their remaining life-expectancy they would trade for living in perfect health compared with their current state. The TTO method was used to create a value set for UK populations from the EQ5D instrument (321). It is considered more likely to have balanced upward and downward biases, thus better reflecting preference for health states than the SG method (320). Either method can be used to determine health utility values.

In sarcoidosis there are no studies comparing generic HRQoL measures, nor has there been any investigating the association between disease-specific measures of health-related quality of life and generic HRQoL measures. There is also limited research investigating the impact of fatigue and depression symptoms on HRQoL; only one previous study has investigated this but using the EuroQoL-5D-3L rather than the 5L (the previous iteration of the EQ5D questionnaire which had shortcomings due to the use of only 3 levels per dimension), with no other generic or disease-specific measurements taken at the same time (313). Comparisons of health status/HRQoL have been made in other chronic conditions, such as rheumatoid arthritis. The health utility scores calculated from the SF-6D, EQ5D and EQ-VAS questionnaires in these patients showed marked differences in agreement between the measurements, as well as a markedly different relationship with clinical parameters and the various utility instruments (322). These differences are also of importance when considering health-economic analysis using these utility instruments, as the choice of instrument would have a large impact on the outcome of any cost-utility analysis.

It is unclear if this difference in utility instrument performance occurs in patients with sarcoidosis given the differences between it and rheumatoid arthritis. In the latter, significant disease activity leads to joint deformity and marked physical disability. By contrast, although progressive and irreversible pulmonary fibrosis does occur in patients with sarcoidosis, the majority will not suffer this outcome. It is more common for patients with sarcoidosis to have ongoing constitutional or non-specific symptoms with potential adverse impact upon quality of life. These constitutional symptoms include fatigue, which has been the focus of this thesis.

As described previously, fatigue is a multi-dimensional symptom with both physical and mental effects. It is unclear whether the severity of this symptom maps onto any of the five dimensions of the EQ5D; if none of the dimensions are responsive to changes in fatigue level then the instrument would not demonstrate any change in health state, and therefore utility value, despite improvements in fatigue. The SF-6D contains the dimension “vitality”, which reflects energy and fatigue levels (319). It is possible that this score would be more responsive to changes in sarcoidosis-

associated fatigue, but this has yet to be proven. Demonstrating whether there is a difference between these instruments in response to fatigue is important; the EQ5D instrument is preferred by the NICE for performing economic evaluations, although NICE state that other instruments can be used when "EQ5D data are not available or are inappropriate for the condition or effects of treatment" (323). Given the concerns regarding the dimensions of the EQ5D, it may be that this tool is inappropriate for reflecting change in sarcoidosis-associated fatigue and that SF-6D should be utilised instead.

Having a better understanding of how the EQ5D and SF-6D perform relative to other instruments measuring clinical problems within sarcoidosis, particularly fatigue levels, will help to better understand how any future cost-utility analysis within the follow-on study from FaST-MP might be affected by the questionnaires included. This knowledge will also help to determine which tools should be included in any future study investigating sarcoidosis-associated fatigue. This study uses cross-sectional data from a large cohort of patients with sarcoidosis alongside the longitudinal health utility data from FaST-MP to answer these questions.

Objectives

To understand the difference in performance between the EQ5D and SF-6D questionnaires through comparing the calculated utility scores from both instruments, and determining the relationship between them and a disease-specific health status measurement (KSQ), fatigue measurement (FAS) and anxiety or depression symptoms (HADS-A).

Primary Outcome:

(1) Compare the health utility scores of the EQ5D and SF-6D within a cohort of patients with sarcoidosis and determine the relationship and level of agreement between the two utility values.

Secondary Outcomes:

(1) Investigate association between health utility scores and disease-specific quality of life scores (KSQ), fatigue (FAS), depression (HADS), and clinical predictor variables (Age, gender, extra-pulmonary disease, use of immunosuppression).
(2) Determine significant predictive clinical factors (disease-specific quality of life scores (KSQ), fatigue (FAS), depression (HADS), and clinical predictor variables) for health utility determined by EQ5D and SF-6D using linear regression modelling.

7.2 Methods

Study design

This is a cross-sectional questionnaire study, which involved administering five questionnaires to patients with sarcoidosis. Data were collected from patients with sarcoidosis under active follow-up at the NNUH, without evidence of another major cardio-respiratory co-morbidity. Patients were contacted via post, with the permission of their treating consultant physician, with a return envelope included with the questionnaire pack and participant information sheet. Alternatively, patients with sarcoidosis who were attending clinic could be given the questionnaire pack whilst attending their clinic appointment and offered the option of completing the questionnaires whilst at the hospital or taking the questionnaire pack away to complete at home and return via post. All questionnaire packs were fully anonymous to attempt to increase the number of patients returning questionnaires.

The data from these patients was analysed along with baseline questionnaire and demographic data from participants in the FaST-MP study. All questionnaires within this study were also administered at the baseline visit for the FaST-MP study, allowing the ability to include pre-treatment data for these sarcoidosis patients to be analysed alongside data from patients returning questionnaires. A target sample

size of 80 patients was pre-specified based upon an achievable sample from patients under the care of the Norfolk and Norwich University Hospital, based upon an eligible cohort of 271 patients (using data from table 18 in chapter 5), and a return rate of 30%, based upon return rates for cohort studies considered feasible (324). It also ensures a minimum of ten data points per variable within the regression analysis.

All subjects were aged 18 or over and able to give informed consent. Ethical approval was gained from the London – Chelsea Research Ethics Committee, REC reference 17/LO/1872, prior to the study commencing.

Study population

For participants recruited for this study the following inclusion and exclusion criteria were used:

Inclusion Criteria:

1. Male or Female aged over 18
2. Diagnosed with sarcoidosis and is under follow-up by hospital, or has been previously, for the condition.
3. Has mental capacity to complete the questionnaires
4. Agreement from primary physician to contact the patient

Exclusion Criteria:

1. Presence of another significant cardio-respiratory disease, major organ disease (except where related to sarcoidosis) or chronic inflammatory condition
2. Unable to give informed consent

There was no restriction on current medications, with data on oral steroid usage, steroid dose, and use of other immunosuppressant drugs collected as part of the demographic data.

Study assessments

Participants within the study were asked to complete five questionnaires in addition to providing data regarding their age, sex, year of diagnosis with sarcoidosis, use of oral corticosteroids (including dose), use of other immunosuppressant medications, and extent of disease (pulmonary disease only, pulmonary and extrapulmonary disease, or extrapulmonary disease only). Participants were then asked to complete the following questionnaires in the following order:

(1) Fatigue Assessment Scale (FAS)
(2) Hospital Anxiety and Depression Score (HADS)
(3) Kings' Sarcoidosis Questionnaire (KSQ)
(4) EuroQoL-5 dimension-5 level (EQ5D) questionnaire
(5) Short Form 36 (SF-36), used to derive Short Form 6-dimension (SF-6D) values

The details and properties of each questionnaire are discussed previously within the methods section for FaST-MP in chapter 4. The questionnaires were chosen to capture data on fatigue levels, disease-related health status, and anxiety and depression symptoms. These factors were considered important based upon the clinical outcomes in the *FaST-MP* study (chapter 4), and that these factors were likely to influence health utility scores derived from the EQ5D and SF-6D questionnaires. All questionnaires can be completed without input from a healthcare professional or research team member.

Utility instruments

Respondents completed the SF-6D and EQ5D questionnaires; results from the EQ5D were directly used to determine health utility values whereas SF36 data had to be converted to six-dimension SF-6D values first. The details of these two instruments has been described previously in chapter 4, section 4.2. The EQ5D consists of five dimensions, each with five potential answers, giving 3,125 potential responses

("health states"). Health utility values less than 0.0, reflecting a health state considered worse than death, are possible from the EQ5D data set. SF-6D is an instrument which can enable translation of SF-36 scores to a health utility score. SF-6D consists of six dimensions (physical functioning, bodily pain, physical role functioning, social role functioning, mental health and vitality), each dimension having between four and six levels. Higher scores within each domain (scored out of 6) indicate worsening function within the dimension. Over 18,000 health states can be described from the SF-6D. Data from each of the instruments can be used to derive health utility values, using existing value sets derived from UK populations; the EQ5D utility values have been previously calculated using the time trade-off method (321) and SF-6D values previously determined using a standard gamble method (319).

Statistical Analysis

All data were transcribed onto a Microsoft excel spreadsheet on a password-protected computer. Values for the FAS and HADS scores were calculated according to the questionnaire instructions. FAS scores out of 50 were stratified into respondents reporting a score >21 (clinically significant fatigue) and >34 (severe fatigue). HADS scores were calculated by tallying the scores within the anxiety sub-score (HADS-A) and depression sub-score (HADS-D); data was then stratified to report the number of respondents with HADS-A and -D scores <8 (normal), 8-10 (borderline) or >10 (anxiety or depression present).

Values from the KSQ were converted to overall sarcoidosis-related health scores within the domains of general health (KSQ-GHS), lungs (KSQ-Lung), medications (KSQ-Med), skin (KSQ-Skin), eyes (KSQ-Eye) and a composite value of each domain (KSQ-GLMSE). In each case, lower scores indicate greater problems relating to sarcoidosis impacting upon the domain. These values were calculated using a custom excel spreadsheet, available from the copyright holder of the questionnaire (273).

Analysis of descriptive statistics (mean and standard deviations or frequencies and percentages) were planned for respondent demographics and questionnaire answers. Number and percentage within each stratum for the FAS and HADS scores were also calculated.

Data from the SF36 questionnaire was converted to SF-6D scores within a custom spreadsheet which calculated health utility values. Responses from the EQ5D and SF-6D were converted to health utility values using excel existing datasets for UK population health utility values. Each patient response for the two questionnaires was converted to a calculated health utility value. The median responses from each dimension of the EQ5D and SF6D questionnaires was calculated; bivariate correlation (spearman's rho given the ordinal nature of the data) was used to calculate the correlation coefficient between each dimension. Utility values from the EQ5D and SF-6D were compared against two global measures of health status contained within two of the questionnaires; the SF36 contains a five-point scale rating health (which is not involved in the calculation of utility scores) that asks respondents to rate their overall health; the KSQ contains a six-point scale rating health asking respondents to score their overall quality of life related to their sarcoidosis. Mean scores for each utility was calculated for each level of the scale.

Distribution of EQ5D and SF-6D health utility scores was checked visually using histograms. Agreement between these two measures was then determined using a Bland-Altman plot. Bivariate correlation, examined by spearman's rank co-efficient (rho), was performed between health status (EQ5D and SF-6D) and both demographics (age, disease duration) and questionnaire scores (HADS-A, HADS-D, FAS and KSQ values). Correlation strength was interpreted according to previous recommendations (325); rho values of 0.3-0.5 were weak, 0.5-0.7 were moderate and >0.7 were strong. Linear regression models were then calculated for each utility instrument to determine which factors were important predictors of health utility values, with predictor variables removed stepwise from the model if their significance was <0.2 at any step until all remaining variables were significant at the 0.05 level; the R^2 statistic was calculated to determine model fit. Only the KSQ composite value (KSQ-GLMSE) was included from the KSQ outputs due to the high

level of interaction between this and other KSQ outputs. This enabled a review of the factors which could be used to predict utility scores for EQ5D and SF-6D, therefore determining which factors the utility scores were responsive to.

Following data entry, a review of missing entries was undertaking; few incomplete questionnaires were submitted, therefore missing data was handled via listwise deletion for any analysis involving the instrument with the missing data point. The exception to this method was the HADS-A and -D scores which had value substitution using the average value of the remaining subset answers (-A or -D), as long as >50% of the questions were answered (326).

All statistical analysis was performed using SPSS Statistics version 25 (IBM Corp, Illinois, USA).

7.3 Results

Participants

One hundred and forty-five questionnaires were sent out to patients, representing the patients who met the criteria for inclusion in the study and had been reviewed in the respiratory clinic during the past 12 months. Of these questionnaires, sixty-eight respondents returned their completed questionnaire pack, a return rate of 46.9%. Additionally, baseline questionnaire data from the twenty-two participants in the FaST-MP study was included, giving a total of 90 datasets from patients with sarcoidosis. The questionnaire completion rate was high, with the SF-36 having the highest number of non-valid returned questionnaires (5/90, 5.5%); 100% of respondents correctly completed the EQ5D. Only one patient each returned invalid data for the FAS and KSQ instruments, although the data completed within the KSQ was still sufficient to provide results for four of the six domains investigated here. The remaining data after list-wise removal was sufficient to perform exploratory regression analysis on the predictor variables for EQ5D and SF-6D utility values.

The demographics for the respondents are shown in table 46. Average scores from respondents for each questionnaire are shown in table 47. A high number of

respondents reported significant fatigue symptoms from their FAS questionnaire, with 65.2% of respondents recording a FAS score of >21, and over a third of those reporting marked fatigue having a FAS score of >34, consistent with severe fatigue.

Table 46 *- Respondent Demographics*

Demographic	**Respondents**
Female sex – n (%)	39 (43.3%)
Age, years – mean (S.D.)	57.0 (11.3)
Stratification by age – n (%)	
<21	0 (0.0%)
21-40	9 (10.0%)
41-60	43 (47.8%)
61-80	36 (40.0%)
>80	1 (1.1%)
Data missing	1 (1.1%)
Disease duration, years – mean (S.D.)	7.4 (8.4)
Pulmonary disease – n (%)	90 (100.0%)
Extra-pulmonary disease – n (%)	52 (57.8%)
Currently receiving steroids – n (%)	36 (40.0%)
Receiving other immunosuppressant – n (%)	15 (16.6%)

Table 47 *- Respondent questionnaire results*

Questionnaire		Result (mean, S.D. unless stated)
FAS		26.5 (10.5)
Fatigue Severity	No fatigue (score 0-21)	31 (34.8)
	Fatigue (score 22-34)	39 (43.8)
	Severe fatigue (score 35-50)	19 (21.4)
HADS – Anxiety	*Mean Value*	7.2 (4.8)
Anxiety symptoms severity	No anxiety symptoms (score 0-7)	50 (56.2)
	Borderline (score 8-10)	16 (18.0)
	Anxiety symptoms present (score 11-14)	23 (25.8)
HADS – Depression	*Mean Value*	5.5 (4.1)
Depression symptoms severity	No depression symptoms present (score 0-7)	63 (70.8)
	Borderline (score 8-10)	14 (15.7)
	Depression symptoms present (score 11-14)	12 (13.5)
KSQ domains		
– General Health Status		58.7 (17.7)
– Lung		61.6 (20.6)
– Medicine		81.2 (23.1)
– Skin		85.6 (22.5)
– Eye		71.1 (22.8)
– Overall (composite) health status		57.8 (11.5)
SF-6D dimensions *(median, range)*		
– Physical functioning		3 (1 – 6)
– Role limitations		2 (1 – 4)
– Social functioning		2 (1 – 5)
– Pain		3 (1 – 6)
– Mental health		2 (1 – 5)
– Vitality		3 (2 – 5)
EQ5D dimensions *(median, range)*		
– Mobility		1 (1 – 4)
– Self-care		1 (1 – 4)
– Usual activities		2 (1 – 5)
– Pain and discomfort		2 (1 – 5)
– Anxiety and depression		2 (1 – 5)

Comparison between EQ5D and SF6D dimension results

Moderate to strong correlation was seen between most of the dimensions of the EQ5D and SF-6D. The strongest coefficient values were seen between SF-6D pain and EQ5D pain dimensions ($r = 0.749$, $p<0.001$), SF-6D mental health and EQ5D anxiety dimensions ($r = 0.730$, $p<0.001$) and SF-6D physical functioning and EQ5D usual activities ($r = 0.722$, $p<0.001$). The remaining correlations are shown in Table 48.

***Table 48** - Correlations between reported patient-reported levels in SF-6D and EQ5D dimensions*

	EQ5D Dimensions				
SF-6D dimensions	**Mobility**	**Self-care**	**Usual activities**	**Pain and discomfort**	**Anxiety and depression**
Physical functioning	0.620**	0.621**	0.722**	0.577**	0.387**
Role limitations	0.518**	0.324**	0.560**	0.443**	0.480**
Social functioning	0.545**	0.483**	0.651**	0.560**	0.609**
Pain	0.606**	0.273*	0.510**	0.749**	0.447**
Mental health	0.235*	0.251*	0.345**	0.329**	0.730**
Vitality	0.491**	0.401**	0.637**	0.458**	0.444**

* = significant at p=0.05 level ** = significant at p=0.01 level

The SF-6D dimension "physical functioning" correlated best with the EQ5D dimensions of "usual activity" and "self-care". "Role limitations" (SF-6D) did not correlate with one single EQ5D dimension, showing moderate correlation with "Mobility" and "Usual activities" but weak correlation with "self-care". "Social functioning" and "usual activities" showed strong correlation, as did the "mental health" and "Anxiety and depression" dimensions. The "pain" dimension of SF-6D and the "pain and discomfort" dimension from EQ5D showed the strongest correlation coefficient of any two dimensions, whilst "vitality" within SF-6D best correlated with "usual activities" in EQ5D.

Utility scores across global measures of health

The performance of each of the individual questionnaires (SF-6D and EQ5D) appeared similar across both general health (SF36) and sarcoidosis-related quality of life (KSQ). Each questionnaire showed good discrimination across levels of health, although differences were seen in performance between each individual questionnaire. The number of respondents returning each level of self-reported health and sarcoidosis-related quality of life are shown in the first row of tables 49 and 50. The EQ5D values were higher across all levels of sarcoidosis-related quality of life and general health compared to the SF-6D values, except in participants reporting very severe problems where the mean EQ5D score was lower than the SF-36 (Tables 49 and 50).

Table 49 *- Utility scores across KSQ-derived self-reported health*

	No problem	Minimal problem	Mild problem	Moderate problem	Severe problem	Very severe problem
No. respondents reporting this level	*19*	*19*	*11*	*27*	*11*	*3*
EQ5D Utility	0.928	0.864	0.833	0.714	0.524	0.351
SF-6D Utility	0.832	0.725	0.689	0.598	0.522	0.501

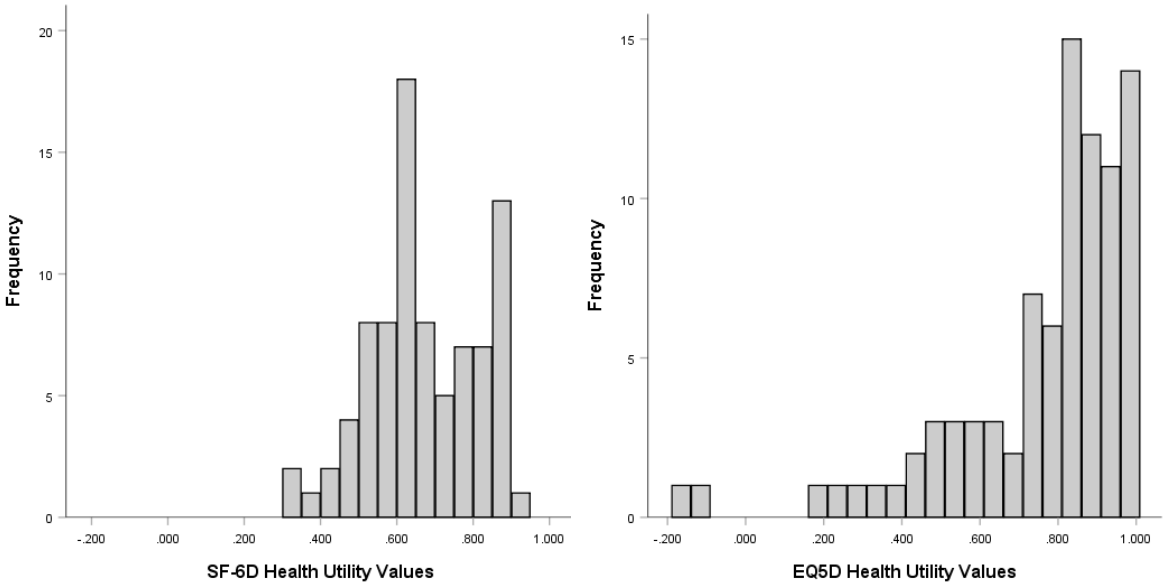
Table 50 *- Utility scores across SF36-derived self-reported health*

	Excellent	Very good	Good	Fair	Poor
No. respondents reporting this level	*3*	*19*	*23*	*26*	*19*
EQ5D Utility	0.966	0.902	0.896	0.713	0.532
SF-6D Utility	0.765	0.799	0.745	0.619	0.511

Distribution of health utility scores

Mean/median scores for the SF-6D and EQ5D scores were 0.671/0.639 and 0.770/0.828 respectively. Two respondents (2.2%) reported an EQ5D utility score of less than zero. All respondents provided data to determine an EQ5D utility score; five patients (5.6%) did not provide sufficient data to calculate an SF-6D utility score. SF-6D values showed a near normal distribution; EQ-5D derived utility values showed a left (negative) skew. Distribution of utility scores across each of the health measures are shown in Figure 21.

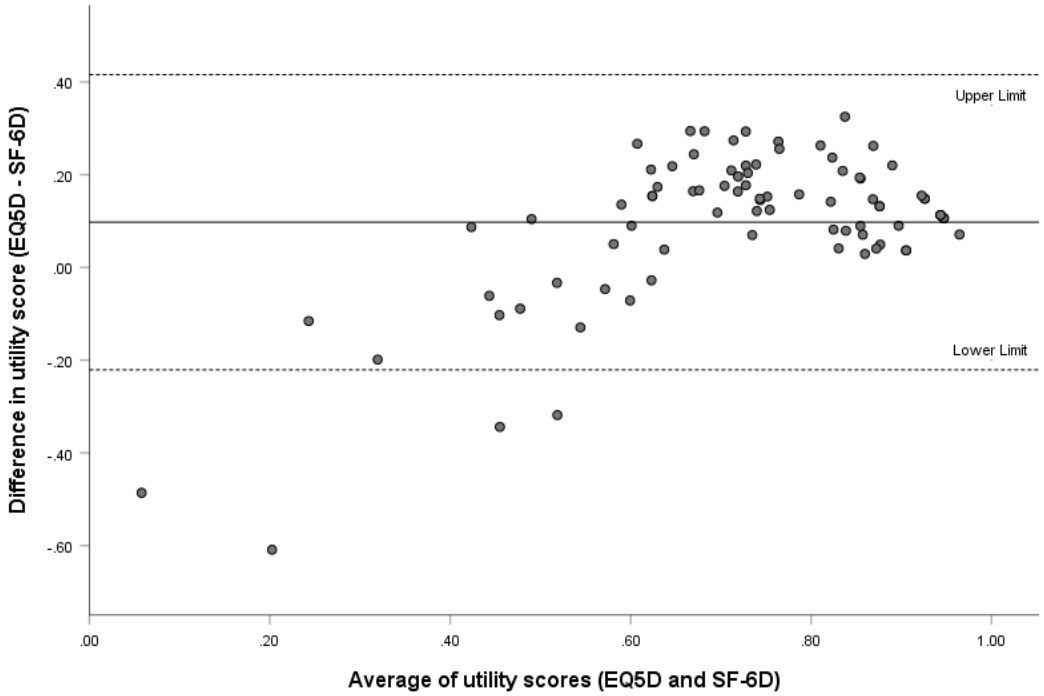
Figure 21 *- Distribution of SF-6D and EQ5D utility values*



Agreement of health utility scores

Agreement between the health utility values derived from EQ5D and SF-6D responses was poor. At poorer health states, the EQ5D utility results are significantly lower than the SF-6D utility scores, whereas at higher health states the EQ5D result is higher than the SF-6D values. Although the average difference between the utilities derived from the two instruments was 0.098, the range in differences between the two values was -0.609 to +0.325. The Bland-Altman plot (Figure 22) graphically illustrates this difference between the results from the two questionnaires, indicating that the bias between the two health utility values was not stable across the range of scores seen.

***Figure 22** - Bland-Altman plot comparing EQ5D and SF-6D utility scores*



Correlations between health utility scores and other clinical markers

Correlations between demographic values and questionnaire results were examined; no dimensions from the SF-6D or EQ5D were included as they would not be independent of the calculated health utility value from the respective instruments. Strong correlation with the health utility scores was seen between general health status, lung and composite domains of the KSQ, anxiety and depression symptoms (HADS-A and HADS-D) and reported fatigue levels (FAS). Moderate correlation was seen with the remaining domains of the KSQ. The demographic data included (age and disease duration) did not show any significant correlation with health utility values (Table 51).

Table 51 *- Bivariate correlation with health utility scores*

	EQ5D	***SF-6D***
Demographics		
Age	*0.055*	*0.131*
Disease Duration	*-0.063*	*-0.085*
Disease Activity		
KSQ-GHS	*0.808***	*0.866***
KSQ-Lung	*0.583***	*0.711***
KSQ-Med	*0.381***	*0.216***
KSQ-Skin	*0.288***	*0.361***
KSQ-Eye	*0.513***	*0.542***
KSQ-Composite	*0.741***	*0.820***
Anxiety and Depression		
HADS-A	*-0.574***	*-0.642***
HADS-D	*-0.677***	*-0.792***
Fatigue		
FAS	*-0.787***	*-0.824***

Values are spearman's rho values
**Significant at 0.05 level*
*** Significant at 0.01 level*

Regression modelling

The results of the linear regression analysis are shown in table 52 (EQ5D) and 53 (SF-6D). Due to high inter-correlated nature of multiple variables in Table 51, and the relatively low number of respondents to the number of variables, only four variables were included in the regression model; FAS, HADS-A, HADS-D, and the KSQ-Composite score. Significant predictor variables only are displayed in the table. Both the FAS questionnaire and HADS-A questionnaire scores were significant predictors for both SF-6D and EQ5D-derived utility values. For the SF-6D utility scores the KSQ-Composite score was also found to be a significant predictor,

indicating perceived physical symptoms and general health status also influenced SF-6D utility scores.

***Table 52** - Regression co-efficients of multiple factors on EQ5D-derived health utility values*

	B	*95% CI*	*p*	*Standardised co-efficient*
FAS	-0.011	-0.016, -0.007	<0.001	-0.507
HADS-A	-0.015	-0.024, -0.006	0.002	-0.292
(constant)	1.180	1.081, 1.279	<0.001	-

***Table 53** - Regression co-efficients of multiple factors on SF-6D-derived health utility values*

	B	*95% CI*	*p*	*Standardised co-efficient*
FAS	-0.005	-0.007, -0.003	<0.001	0.392
HADS-A	-0.008	-0.011, -0.004	<0.001	-0.248
KSQ-Composite	0.005	0.003, 0.007	<0.001	0.387
(constant)	0.588	0.425, 0.751	<0.001	-

The following predictor equations were derived using the linear regression results:

- EQ5D Utility = 1.180 - 0.011 x FAS – 0.015 x HADS-A, **adjusted R^2 = 0.492**
- SF-6D Utility = 0.005 x KSQ-Composite - 0.005 x FAS – 0.008 x HADS-A + 0.588, **adjusted R^2 = 0.793**

Of the significant predictor variables for each HRQoL score's derived utility values, the FAS score had the strongest effect on EQ5D-derived utility values (standardised coefficient -0.507), whilst the KSQ-Composite scores and FAS scores had similar effects upon SF-6D-derived utility values (standardised coefficients 0.392 and -0.387 respectively). Overall, the model for SF-6D utility values predicted 79.3% of

variance seen, whereas the EQ5D model only explained 49.2% of variability in the derived utility scores.

7.4 Discussion

Relative performance of the EQ5D and SF-6D

Comparing the individual dimensions of the EQ5D and SF-6D shows that there are dimensions that behave similarly and are therefore likely to measure the same aspects of health status. Some show strong correlation coefficient values between single dimensions in each instrument, such as “pain” in SF-6D and “pain and discomfort” in EQ5D, or “mental health” in SF-6D and “anxiety and depression” in EQ5D. These dimensions are very similar, and it is unsurprising that they show good correlation. Some dimensions of the SF-6D have no single equivalent in EQ5D, so moderate correlation at best was seen with multiple EQ5D dimensions. This was particularly noticeable with the “role limitation” and “vitality” dimensions in the SF-6D, where the dimension encompasses both physical and mental condition, although the vitality dimension showed moderate correlation with usual activities. Given that the vitality domain reflects energy and fatigue level, the correlation between scores within these two dimensions supports the suggestion that fatigue and activity levels in free living are related (327), although the correlation coefficient between these dimensions was moderately strong (rho = 0.637). Overall, the lack of a specific dimension in EQ5D equivalent to the vitality dimension in SF-6D suggests that SF-6D health states and derived utility values are more likely to be responsive to changes in fatigue levels within an individual.

The spread of utility scores derived from the EQ5D suggests that there is a ceiling effect with the utility values from this instrument, something which has been suggested from previous studies (328). This may mean that the instrument is less able to discriminate between people in fair health when compared with the SF-6D. The results showed that a significant number of respondents had a utility score of 1.0 with a skewed distribution towards higher values. This occurred despite the patient cohort within this study being more likely to be suffering chronic disease or

extrapulmonary disease compared with non-respondents. The reason for this ceiling effect may be due to the dimensions included in EQ5D not being responsive to chronic symptoms from sarcoidosis due to constitutional symptoms such as fatigue or small fibre neuropathy. The increased number of dimensions within SF-6D (six) compared with EQ5D (five), and therefore the higher number of potential health states available (18,000 and 3,125 respectively), may explain why the SF-6D appeared better able to respond to variations between patients which was seen in this study. The greater number of health states gives greater resolution and greater ability to differentiate health states within patients, particularly in milder disease where the EQ5D appeared to have a ceiling effect.

The observed distribution of health utility values from the SF-6D utility values was markedly different to those calculated from the EQ5D results, with the score behaving differently at the extremes compared with the SF-6D. Whilst SF-6D and EQ5D values all individually showed good discrimination across self-reported health states related to general health and sarcoidosis-related health (Tables 49 and 50), there was poor agreement between EQ5D and SF-6D utility values. Differences in utility scores over 0.5 are seen between the two instruments, a large difference considering the scale of possible health utility values permitted by the instruments. The size of the difference between the two instruments was seen to vary in size depending on the health state of the patient (shown in the Bland-Altman plot, Figure 22). This finding has been identified previously in other conditions, including rheumatoid arthritis (322) and chronic pain (329). This may be related to the extended range of the EQ5D, where it is possible to give responses that equate to a health state perceived as worse than death. However, it should be noted that the EQ5D score showed a skew towards higher values rather than lower ones, and only two respondents reported EQ5D scores corresponding to a utility value of less than zero.

An alternative explanation is that the health utility score calculations for EQ5D and SF-6D were performed in different ways; the SF-6D values were calculated using the SG method whilst the EQ5D values were determined using a TTO method. The biases present in each method are different, leading to variances in utility values

calculated by the two methods. The SG method is thought to suffer upward bias, giving a higher utility value for a given health state compared with the TTO method (320). Unfortunately, no UK-derived utility value sets using the TTO method are available for the SF-6D questionnaire to allow direct comparison with the EQ5D value sets, although the SF-6D-derived health status values observed here were lower than those derived from the EQ5D questionnaire results, suggesting that the known biases between the SG and TTO methods of deriving health utility are not responsible for the difference seen. This makes it more likely that the disparities are due to how the dimensions within the EQ5D and SF-6D instruments respond to differences in clinical factors, including fatigue.

Predicting utility values from other measures

Regression models were able to predict SF-6D values with a good degree of fit; the adjusted R^2 value of a model containing the KSQ-composite, HADS-A and FAS scores was 0.793, suggesting that almost 80% of variability in the calculated utility score from SF-6D was explained by the model. By contrast, the model for the EQ5D was able to predict less than half of the variability seen in the utility scores from the predictor variables captured in this study.

Fatigue has previously been shown to correlate with lower EQ-VAS scores (313) but had not been compared with utility values derived from the questionnaire. This study has allowed the opportunity to do this. Fatigue, as measured by the FAS score, was found to be a significant predictor for both SF-6D and EQ5D values. It was hypothesised before the study began that this may not be the case due to the difference in the dimensions contained within the EQ5D and SF-6D instruments. SF-6D features the dimension “vitality”, which is derived from a question pertaining to energy levels and activity. Despite this, the EQ5D was still responsive to levels of fatigue reported by respondents. Both scores were also responsive to changes in anxiety (HADS-A) scores. The SF-6D utility scores were also impacted by changes in the composite KSQ score, reflecting the overall score from the KSQ incorporating multiple disease-related issues including general health status. This would have

been the measure most likely to reflect physical symptoms and suggests that the SF-6D utility score may be more likely to reflect changes in disease severity.

The results from the cross-sectional data suggest that the SF-36 questionnaire from which SF-6D health states are derived should be considered an appropriate and responsive instrument for measuring health utility in patients with sarcoidosis. Alternatively, the shorter SF-12 questionnaire could also be used as the SF-6D health states can also be derived from this tool and is a third of the length of the SF-36 questionnaire. The SF-6D utility score appears to be responsive to changes in disease-related health status, anxiety symptoms and fatigue severity, all of which are important variables in any study investigating patients with sarcoidosis, whereas variation in the EQ5D utility score was only explained by two of these three important factors.

Strengths and limitations

This study included a well-defined sarcoidosis cohort from a hospital outpatient roster, ensuring that patients with a secure diagnosis of the condition were included. There was also a good return rate for a postal questionnaire, with almost half of the patients contacted returning the questionnaire pack. This cohort of patients contained a range of disease severities, with a tendency towards wider disease involvement given the number of patients reporting extra-pulmonary disease and the use of immunosuppressant medications. This cohort also included a large number of non-fatigued patients, allowing a wider understanding of how these questionnaires perform across levels of fatigue, not just in patients with significant fatigue as was the case in the *FaST-MP* study (chapter 5). Directly comparing the EQ5D and SF-6D questionnaires in patients with sarcoidosis has enabled differences in the performance of the two measures to be identified.

This study had a number of limitations. It contained patients recruited from a single centre only, although this was chosen deliberately to ensure a well-defined cohort was included. This meant that the cohort was small compared with other cohort studies in other chronic diseases, which have included over a thousand participants

(322). The included patients tended towards more severe disease and older age, although this may be related to the demographic in the Norfolk area. The data was also from a single time-point only. Performing repeated measurements would have allowed an exploration of the changes between fatigue scores and calculated utility values over time. This would have allowed insight into how the change in one response would relate to the other. Finally, the data collected was anonymous, a decision taken to try and maximise the response rate from patients. This did mean that the data could not be linked back to individual clinical parameters, such as pulmonary function and radiological staging.

7.5 Conclusions

The HRQoL instruments measured in this study varied in their performance; to explain this it is important to consider that HRQoL is a multi-dimensional construct which is affected by a multitude of factors, including disease-related factors and symptoms (223), personality type (330), and mood (331). Within patients with sarcoidosis, HRQoL can be impaired by problems with mobility, working capacity, cognitive aspects, sleep, social interaction, depression and issues with usual activities (332). Not all patients will have impairment in HRQoL due to all of these aspects; the optimum instrument to measure HRQoL should be responsive to all of these factors. In this study SF-6D appeared responsive to more factors than EQ5D and so should be considered preferable to EQ5D for measuring HRQoL, and calculating health utility, in patients with sarcoidosis.

With this chapter, additional data has been presented for the performance of the various questionnaires. The outcomes support the use of SF-6D over the EQ5D in trials enrolling patients with sarcoidosis, given that the measure appears to be responsive to a greater number of important factors in patients with sarcoidosis, notably fatigue, anxiety and disease-related quality of life. Alongside data gathered from the *FaST-MP* study (chapter 5) and feedback from participants during focus group discussions (chapter 6), the results from this study help to inform the choice

of outcome measures for any future study investigating treatment for sarcoidosis-associated fatigue.

In the next chapter, the results from all the studies undertaken in this thesis are discussed, leading to a proposed design for a future study to determine the clinical efficacy of neurostimulant agents for sarcoidosis-associated fatigue.

Chapter 8 – *Discussion*

8.1 Introduction

The work presented in this thesis has demonstrated the limited current evidence for interventions targeting sarcoidosis-associated fatigue, and undertaken research to determine how to design and perform a full randomised-controlled trial to determine the clinical efficacy of methylphenidate for treating sarcoidosis-associated fatigue. This chapter concludes the thesis by considering what was discovered throughout this project, and reflecting on how the lessons learnt could influence future work in this area.

8.2 Fatigue as a feature of sarcoidosis

Prior to the undertaking of this thesis, fatigue had been identified as a common symptom affecting patients with sarcoidosis (122), including work already undertaken by the author in a cohort of patients with sarcoidosis who were under the care of the Norfolk and Norwich University Hospital (170); that research, performed as a cross-sectional study of patients attending the respiratory clinic with a diagnosis of sarcoidosis, identified that 50.7% of cases reported significant fatigue when scored using the FAS questionnaire, and that these participants were more likely to report symptoms of mental fatigue. The research themes addressed within this thesis directly stemmed from that earlier work, and whilst it was not a primary objective of this thesis to replicate and confirm these earlier findings, it is reassuring to see that the findings presented in this thesis support these previous results.

Two of the projects undertaken within the thesis collected data that enabled estimation of fatigue rates within the cohort of patients at the Norfolk and Norwich University Hospital. In the screening log for the *FaST-MP* study, 43.9% of participants were identified as reporting fatigue; this was lower than the earlier study but included all participants under the care of the respiratory clinic, including those who had mild disease (stage I) or incidentally discovered disease, and may be less likely to suffer significant fatigue. Alternatively, the lower rate may represent an under-reporting of fatigue within clinical notes. By contrast, the rate of fatigue

reported in chapter 7 (*A comparison of measurements of health-related quality of life in patients with sarcoidosis*) was higher than previously identified, with 65.2% (58/90) of respondents reporting a FAS score of >21, consistent with significant fatigue. However, the data for 22 of these participants came from the *FaST-MP* study; with this data removed, the reported fatigue rate in the remaining group was 52.9% (36/68 respondents), almost identical to earlier work. Fatigue therefore remains a high burden and one with a significant negative impact upon quality of life for patients suffering this symptom.

Beyond reported quality of life, fatigue itself appears to reduce levels of physical activity undertaken. In Chapter 3 (*Determining a preferred measurement device for recording daily activity in patients with sarcoidosis*) the data collected from participants undertaking a cross-over study of two wrist-worn activity monitors was analysed to compare fatigue levels (measured using the FAS questionnaire) with recorded levels of activity and sedentary behaviours. Despite the small numbers undertaking the study, the data did support at least moderate correlation between daily time spent performing sedentary activities and fatigue scores, with increasing fatigue leading to increased sedentary time. As patients become increasingly sedentary this in itself may increase fatigue, propagating a cycle which leads to ever worse activity, fatigue and quality of life.

When considered alongside the negative impacts seen in patients suffering significant fatigue, the results reinforce the importance of treatment of this debilitating symptom. The rationale for introducing treatment in patients with sarcoidosis is moving towards one of treating for two reasons; risk of long-term damage to organ function or risk of unacceptable impairment to quality of life (82), with the latter fitting with the impact of fatigue on patients' lives. The current evidence base for any form of treatment for sarcoidosis-associated fatigue is weak. This was the rationale for undertaking the work presented here, aiming to move a step towards undertaking appropriately designed studies that may help to determine the optimum management strategies for patients with sarcoidosis-associated fatigue, including the role of methylphenidate for symptom management.

8.3 Methylphenidate as a therapeutic option for sarcoidosis-associated fatigue

Previous data supporting methylphenidate use

The evidence base for possible interventions for sarcoidosis-associated fatigue was discussed in chapter 2, with limited evidence available for any single approach to managing this difficult symptom. Neurostimulants, such as methylphenidate, were a promising therapeutic option where sarcoidosis activity was not deemed sufficient to require systematic therapies such as corticosteroids or, in severe disease, anti-TNF-alpha agents; these drugs often risk significant side-effects of their own. There was an unmet need in the respiratory clinic for effective management strategies for sarcoidosis-associated fatigue, including the use of neurostimulants, but the evidence base for their use was limited.

A single previous trial had investigated the use of methylphenidate for patients with sarcoidosis-associated fatigue; Lower and colleagues used dexmethylphenidate, the d-isomer of methylphenidate, for symptomatic relief of sarcoidosis-associated fatigue (173). This work took place on the back of earlier work investigating the effectiveness of dexmethylphenidate for cancer-associated fatigue post-chemotherapy, which had suggested benefit compared with placebo over an eight-week period (211). In the trial by Lower and colleagues, the clinical outcomes suggested a benefit compared with identical placebo, with a mean drop of five points in the FAS score over an eight-week treatment period. The study was small, including only ten participants, and measured outcomes over a short period of time (8 weeks). This sample size was insufficient to prove the clinical efficacy of methylphenidate. Furthermore, the potential weaknesses of a cross-over study design, as discussed in Chapters 4 and 5, meant that there would have been difficulties maintaining participant blinding, as well as the possibility of carry-over effects through the wash-out period. On this basis, the *FaST-MP* study was designed to increase the evidence base, primarily with the aim of informing the design of trials sufficiently large to determine the efficacy of methylphenidate, or alternative neurostimulants agents.

Several features from the earlier cross-over study were used as the basis for *FaST-MP*; the dose range of methylphenidate chosen was equivalent in action to the dexmethylphenidate doses used, and the fatigue outcomes used were the same as the earlier trial, which would allow direct comparison of changes in scores. The inclusion criteria were modified slightly; the requirement to have had a diagnosis of sarcoidosis for at least two years was not included, allowing participants with a recent diagnosis to be randomised, and participants were also required to have a minimum level of fatigue according to the FAS score, in an effort to ensure that patients with more severe fatigue were included. The main difference however was the decision to design the study as a parallel-arm rather than cross-over trial, as well as extending follow-up for a 24-week period. These decisions were made for two reasons. Firstly, the parallel-arm design aimed to overcome the challenges of maintaining blinding in a cross-over study when using a symptom-targeting treatment (which was thought to have potentially obvious effects for patients). The increased duration was used to look for persistence of effect beyond 8-12 weeks, the duration which trials investigating methylphenidate for a number of indications had thus far used for follow-up. It was also unclear how many patients with sarcoidosis would be eligible for the study, or wish to participate; the earlier study by Lower et al found that 10 out of 44 patients assessed (22.7%) were eligible and willing to participate, but it was unclear if this would be replicated in the respiratory clinic of a medium-sized tertiary hospital.

Outcomes from the FaST-MP study

Recruitment to the *FaST*-MP study was lower than anticipated, with only 55 patients of the 385 assessed for eligibility (14.3%) meeting the criteria for inclusion in the study, and only 22 of those patients (40% of those eligible, 5.7% of the total patient cohort assessed) agreeing to participate in the study. This therefore represents a small percentage of patients with sarcoidosis who would be eligible for participating in future studies if the same inclusion and exclusion criteria were used.

However, a number of positive factors were identified. Of the 19 participants surveyed at the end of their participation in *FaST-MP*, all reported the trial as having been a useful experience for them, and would recommend participation in similar future trials to other patients with the condition. Participant retention through the trial, as a result, was excellent. Although one participant had to discontinue study medications due to side effects, no participants withdrew from the study and all attended the full number of trial visits. The use of activity monitors was also a promising outcome, with most participants successfully wearing the devices sufficiently to gain valid data for analysis. Another encouraging outcome was the well-tolerated nature of the methylphenidate, with no evidence of problems with hypertension or sleep abnormalities occurring in the methylphenidate group. Despite the small number of eligible patients, the data does support feasibility of future studies in this area, although to recruit sufficient participants to determine clinical efficacy will require studies to be active across multiple sites, preferentially large tertiary centres with large cohorts of patients with sarcoidosis under ongoing care.

The clinical outcomes from the *FaST-MP* study were unexpected, although these were not the primary outcome of interest. The between-group performance revealed no persistent significant difference between the placebo and methylphenidate arms across most outcomes, with a tendency towards improved performance in the placebo group; this was the case in the fatigue score outcomes, where the mean values appeared to indicate lower fatigue levels in the placebo group. Some outcomes reached a statistically significant difference between arms; anxiety (HADS-A) and health utility values (SF-6D and EQ5D) were improved in the placebo group, whilst sedentary behaviour time (minutes per day) improved in the methylphenidate group. When interpreting the results, it is important to consider that the *FaST-MP* study was never designed or powered to detect evidence of clinical benefit for methylphenidate compared with the placebo arm; the primary outcome was to determine the feasibility of future work, not to confirm clinical efficacy.

Lessons the FaST-MP study

The potential reasons for the unexpected results were discussed in Chapter 4, and may relate to a number of factors. These include the small size of the placebo group, the large amount of clinical contact with the research team acting as an intervention itself, reduced anxiety in the placebo group which may have been negated in the methylphenidate group due to common side-effects of the medication, an increased level of physical activity seen in the methylphenidate arm leading to increased physical exhaustion and fatigue despite achieving more, or potential biases in the study population including the presence of demand characteristics. The post-hoc analysis of data did not support the inclusion of participants with a recent diagnosis of sarcoidosis causing issues due to spontaneous resolution in these patients.

Despite the lack of mean improvement seen in the methylphenidate group relative to the placebo group, it is important to consider other results when evaluating whether methylphenidate could be a useful treatment for sarcoidosis-associated fatigue. Firstly, the proportion of participants in each arm who wished to continue taking their allocated intervention at the end of the study was higher in the methylphenidate arm than the placebo arm (91.7% vs 71.4%), indicating a high level of satisfaction and perceived benefit from methylphenidate. Secondly, in the data collected within the focus groups, presented in Chapter 6, a number of participants in the methylphenidate group reported significant improvements compared with their baseline level of function, without reporting any significant problems associated with taking the medication. Finally, concern was also expressed within the focus group participants that the outcome measures, including the fatigue questionnaires chosen, did not necessarily reflect what they considered to be significant changes in levels of fatigue. This may mean that the outcome measures being assessed here do not reflect the number of participants who perceived significant benefit whilst receiving medications.

The ability to maintain blinding was also reassuring. During the study there were concerns that blinding would be impossible to maintain due to clear positive clinical effects or characteristic side effects from the medication. The results from the *FaST-*

MP study suggested that participants were reasonably accurate at identifying their allocated group (81.8% accuracy across both groups), although they were much more accurate at identifying if they had received methylphenidate (93.3% accuracy) than if they had received placebo (57.1% accuracy). This is reassuring as it suggests that blinding can be maintained to an acceptable extent, but also reinforces the importance of any placebo-controlled study being of a parallel-arm design as participants would likely be able to identify when they received the active drug in a cross-over study, defeating the blinding and potentially altering the results.

The overall performance of the methylphenidate arm relative to the placebo arm should not preclude future trials being performed in this area, although it should lead to detailed consideration of the study design. Choosing the ideal outcome measures and eligibility criteria are two key issues facing future studies, which are discussed in more depth in Section 8.5.

8.4 Difficulties encountered within this thesis

Although a number of linked projects were undertaken within this thesis, the main study, *FaST-MP*, was the only project that presented a number of problems. Whilst some of these issues became apparent with unblinding and analysis of the data, relating to the unexpected results in the exploratory clinical outcomes, there were difficulties encountered before the trial opened and whilst the trial was being undertaken. This has led to important lessons being learnt throughout this PhD relating to the undertaking of clinical trials and the importance of proper resourcing in terms of staffing and facilities.

The first difficulty related to the final trial design. The initial design for the *FaST-MP* study planned for participants to meet with the study team fortnightly for the first six-weeks to establish a stable medication dose. Following this, participants would be seen six-weeks later (at week 12) to check adherence, safety and efficacy, and then would not be routinely reviewed until week 24, the final study visit. This structure was chosen to attempt to closely replicate usual care, where contact with the clinical team would not be more frequent than 6- or 12-weekly once

established on medication. In order to obtain clearance from the research ethics committee to undertake the study, the frequency of participant visits was changed. In addition to the planned visits, an additional visit was added at week 18, with phone calls added between each visit (see chapter 4 for the final study design), which meant that participants were never left more than 2 weeks without contact with the study team. These design changes meant that the placebo arm no longer reflected "usual care" as there was a significantly higher level of interaction between participants and the study team. This may have changed the behaviour of the placebo arm, both because the increased contact acted as a form of intervention on its own, reducing anxiety in participants, as well as potentially introducing bias in the form of demand characteristics. This latter issue may have been further affected by limitations in the number of trained staff to perform study activities and visits.

Despite the study being registered on the NIHR clinical research network's portfolio, which meant that funds were made available to provide research nurse support, there was great difficulty recruiting and retaining auxillary staff whilst *FaST-MP* was being undertaken. This led to the author running the study on a single-handed basis for large periods of time, undertaking research visits with trial participants and performing all trial management duties. Whilst running a trial in this manner allowed a full understanding of the amount of work a clinical trial of an investigational medicinal product is, even a small feasibility study, and provided invaluable learning opportunities relating to the management of a clinical trial from conception to completion, it also may have had negative consequences on the study itself.

As a result of the lack of additional support, all study visits and most phone calls to participants were undertaken by the author. This fostered an excellent relationship with the participants but may have provided overly optimistic estimates of questionnaire completion rates and retention rates, with participants less likely to withdraw from the study despite an onerous visit schedule over a six-month period. The level of interaction has also been suggested as a possible reason for the better than expected performance of the placebo arm; with frequent interaction with the

author, functioning as both a researcher and clinician, this may have led to significant reduction in anxiety in participants in the placebo arm through the knowledge that they were in close contact with a member of the clinical team, and were able to contact them at any time whilst participating in the study.

Beyond the reassurance of increased contact with the research team and, by extension, the clinical team, the possibility of bias from demand characteristics influencing the outcomes cannot be excluded. The risk from having one investigator performing all study visits, and therefore having contact with each participant at all visits, is the development of a relationship that may impact upon the perception of participants towards the study and its aims. The risk may have been exacerbated by the participants being aware that the research study formed a large section of the investigator's research thesis. Despite the double-blind design of the *FaST-MP* study, it is still possible that the presence of demand characteristics may have influenced participant behaviours and outcomes. One indication that demand characteristics may have been able to influence outcomes was the discrepancy in the number of participants who were able to correctly guess their treatment allocation at the end of the study. A higher proportion of participants in the placebo group incorrectly identified their allocation, suggesting that they believed they were on the active medication, and therefore behaved as if they were receiving medication, including attempting to prove the study hypothesis as a "good participant" (291). The original work on demand characteristics by Martin Orne recommended the use of multiple experimenters as a way of controlling for such characteristics (333); due to issues relating to staff trained or available to undertake the study visits this was not possible within the study. Whilst the considerations of demand characteristics are particularly applied to psychological research, it is possible that influence could be exerted on an outcome measure such as fatigue, which can only be recorded as it is perceived by the participant. The role of participant demand characteristics should therefore not be excluded.

Additional problems were encountered in securing appropriate facilities to undertake one of the clinical outcome measures. The MSWT had been chosen as a clinic-based outcome of exercise capacity as it is a maximal-effort test, which was

felt to be most likely to yield changes over time with increases in fatigue given that reduced fatigue may lead to increased volition, effort and exercise capacity. Whilst the test requires a shorter track than a six-minute walk test, another clinic-based measure of exercise capacity, participants increase their pace throughout the test, ending at a running speed once the later levels of the test have been reached. The increased speed of the participants performing the test meant that a larger space was required to safely undertake the test. Identifying such a location within the hospital proved difficult, with only the clinical research and trials unit having sufficient space to undertake the tests. When discussing the outcome measures with participants in the focus groups, they considered the location to be inappropriate; the location was not considered fully safe with office equipment near the area, and other staff members not participating in the research occasionally crossing the course unexpectedly. Despite this, the tests were completed without injury until the research and trials unit was moved within the hospital, leading to a loss of the space for undertaking the MSWT. As a result, only participants 1-16 have at least two completed MSWT values; the remaining participants were unable to complete a second MSWT. This finding clarified the difficulty in identifying sufficient space in hospitals for undertaking tests such as the MSWT and, as suggested by participants in the outcomes from the focus groups in Chapter 6, maximal exercise tests would be more appropriately performed on a static piece of equipment such as an ergometer or treadmill. Performing MSWTs in multiple centres, unless they have access to a sports hall or gym, may not be feasible; the ability to use static tests such as cardiopulmonary exercise testing is likely to be more practical to deliver and standardise across multiple sites, and provide more information on participants' cardio-pulmonary performance and exercise capacity.

8.5 Considering a future Phase III study

This thesis set out to investigate several factors that would determine the feasibility of performing a sufficiently large RCT to provide evidence for the clinical efficacy of methylphenidate, or an alternative neurostimulants, for the treatment of

sarcoidosis-associated fatigue. The outcomes from this thesis provide important details on factors that would need to be changed or implemented for a future randomised controlled trial investigating symptomatic treatment of sarcoidosis-associated fatigue.

DESIGN – Whilst earlier studies have utilised a cross-over design (173, 334), the high proportion of participants who were able to determine their allocation based on their experience whilst receiving methylphenidate shows that a parallel-arm RCT design would be required for any future study. Maintaining blinding effectively in a cross-over study would not be possible. Reducing the number of visits and telephone contacts with participants may also be beneficial. The amount of contact was mandated due to concern that side effects may arise and would not be identified or reported without close monitoring and follow-up. During the study any adverse events that did occur were reported between visits; participants were able to contact the research team in the event of problems and seemed to be able to reliably do this. Designing a follow-up study with a reduced number of visits seems reasonable given the findings related to the reporting of adverse events.

INTERVENTION – Methylphenidate was used as the intervention for *FaST-MP* and appeared to be well-tolerated. Future studies should consider an increased maximum dose. Within *FaST-MP*, the maximum daily dose was 20mg twice daily (40mg per day), in keeping with the dose regime used in the earlier cross-over study (173), and was well tolerated. Studies investigating methylphenidate for other conditions, including fatigue related to traumatic brain injury (335), cancer (336) and HIV infection (213) have used higher maximum doses (54-60mg per day) which were well tolerated. The option to use a higher maximum dose in participants who tolerate 40mg per day is within the acceptable dose range for methylphenidate, has evidence for earlier work in other interventions, and would ensure that an effect for methylphenidate is not missed due to the selected dose range being too low. For these reasons, a dose range of up to 60mg/day is recommended for future studies.

One consideration discussed in the conclusions of the *FaST-MP* study was the use of a psychological intervention to manage anxiety in patients where this is a significant

driver of their fatigue. Whilst this would require a two-stage design, with participants undertaking the psychological intervention prior to being randomised to receive methylphenidate or placebo, it would ensure that those included in the trial were those who were most likely to benefit from the use of neurostimulant medication directly targeting fatigue.

CONTROL ARM – One of the main lessons learnt from the *FaST-MP* study surrounded the importance of the control arm being a fair reflection of usual care; the number of study visits included in *FaST-MP* was a shortcoming, one which may have affected the performance of the placebo group (see previous section). Suggestions have been made regarding a control population that is drawn from clinic but do not participate in study visits, thereby being more likely to behave as a patient receiving "usual care" would. Whilst this would be feasible this would not control for a placebo effect, something which would need to be controlled for given the performance of the placebo arm seen within the *FaST-MP* trial.

SAMPLE SIZE – No difference in fatigue scores, either FAS or FACIT-Fatigue, were seen between the study arms; the results seen tended to favour placebo overall. However, the *FaST-MP* study was designed to answer questions surrounding the feasibility of a future study, therefore the clinical outcomes observed in either arm should not be read into too much. The FAS score appears to be a reasonable primary outcome given that it is validated in sarcoidosis and has been used in other studies so it allows direct comparison of results; on this basis, powering for the MCID of 4 points requires a sample size of 120 patients. Participant retention in the *FaST-MP* study was excellent, possibly relating to the single investigator reducing the likelihood of participants withdrawing, so an additional 10% to cover for a higher drop-out rate in a larger study would be reasonable to reduce the risk of drop-outs leading to an unacceptable reduction in statistical power to detect a between-group difference. The total sample required would be 134 patients, based on a between-group difference in FAS of 4 points, a mean baseline FAS score of 33.9 with a standard deviation of 7.8 (taken from the baseline FAS scores across both arms), 80% power and a significance level of 0.05, and an anticipated drop-out rate of 10%. This number of patients would be feasible from only a few centres

around the country if they were large centres with big cohorts, given that it was possible to recruit 22 patients from Norwich alone with a cohort of patients with sarcoidosis numbering fewer than 400, albeit with an enthusiastic clinical fellow which may have increased the recruitment rate.

ELIGIBILITY CRITERIA – Previous work (173) excluded participants who had been diagnosed with sarcoidosis for less than two years prior to study entry, to ensure that participants included were more likely to have chronic fatigue that was unlikely to spontaneously resolve. A minimum duration of disease was not specified for the *FaST-MP* trial, although sub-analysis of those having the disease for a minimum of 1, 2 or 3 years did not modify the results of the fatigue data (see Figure 20 in Chapter 5). Ensuring the robustness of patient characterisation, through minimising the risk of spontaneous resolution of fatigue in patients who have fatigue as part of the acute presentation of sarcoidosis, may lend weight to the use of a minimum disease duration at study entry. Even with this included as part of the inclusion criteria, the projected sample size to investigate clinical efficacy would still appear feasible based on the small number of participants required from the sample size calculations, therefore a minimum disease duration of 1- or 2-years should be specified in addition to the inclusion and exclusion criteria from *FaST-MP*.

DURATION – Previous work with methylphenidate has used shorter follow-up; the *FaST-MP* study used a longer duration to investigate whether there was any suggestion that the anti-fatigue effect of methylphenidate may drop-off, with the results showing no evidence of it. A shorter duration is likely to be all that is needed to confirm an effect in a future study.

QUESTIONNAIRE OUTCOMES – The outcomes from *FaST-MP*, with the additional data collected from individual participants in the focus groups following their trial participation, provides much insight relating to the optimal questionnaires to use in future trials. Participants in the focus groups were keen to see the number of questionnaire outcomes reduced. Within the questionnaire pack used in *FaST*-MP there were several outcome measures that would not be necessary in a future trial.

Participant-reported fatigue, measured using questionnaires, would remain a key outcome but the data collected suggests that it is not necessary to use two questionnaires; both the FAS and FACIT-Fatigue questionnaires showed the same pattern of change across the *FaST-MP* study. Concerns about the negatively marked questions in FAS appear unfounded; as long as participants are clearly informed about the negatively marked questions in FAS, this questionnaire could be used on its own for fatigue outcome.

Alongside this, to allow cost-utility evaluation, a measure of HRQoL would be beneficial. Data from both *FaST-MP* and the HRQoL comparison study suggest that SF36 has benefits but is longer. This questionnaire could be cut down to the SF-12, one third of the length, which still includes questions on vitality and can be converted to SF-6D health states, from which a utility value can be derived. EQ5D is therefore not required.

Measuring anxiety is clearly important as it was one factor that changed markedly over the study duration in the placebo arm; HADS appears reasonable to track this. Finally, factors affecting disease-specific health state also differed between arms and changed over the course of the study; the KSQ proved its worth in this regard. These four questionnaires (FAS, SF-12, HADS and KSQ) would require a significantly reduced time to complete.

The sample size suggested was calculated based on the MCID of the FAS score, but concerns were raised during the focus groups that this may not be the ideal outcome measure; some participants were concerned that it was not responsive to what they considered a significant improvement in their fatigue levels. A simple scale may be preferred and could be administered more frequently by participants. Fatigue levels could be measured using simple measures, such as a visual analogue scale or a five-point likert scale, and could be recorded once or twice a day by participants. This could be done via a fatigue diary, with participants recording their daily fatigue score at the same time each day within the diary, or through the use of electronic devices which could log the score each day. This would provide a much greater resolution of fatigue data; if this were to be done via an electronic device

for each participant, it could also influence which devices should be used for collecting activity data.

DAILY ACTIVITY OUTCOMES - In the FaST-MP study it appeared feasible to use activity monitors at multiple points during the study. However, in the time it has taken to complete the work on this thesis, having piloted potential devices and settled on the GENEActiv device as the preferred option (which did reliably collect data within the context of an RCT), wearable technology has moved on significantly. Devices such as the latest version of the Apple Watch (Apple Inc, Cupertino, CA, United States) could allow both the recording of activity, potentially even on a daily level through the entire study, as well as collection of simple outcome data for fatigue levels. These devices have been shown to accurately measure steps, heart rate, distance and sleep patterns (337). In addition to these factors, the latest versions of these devices can record location and movement via global positioning software (GPS), which has been used to monitor activity patterns in trials previously (338, 339) and would provide additional benefit on the change in activity participants experience during such a trial.

Using a device fulfilling such criteria would give a much greater resolution of data, could provide data on the kinds of activity an individual is undertaking during such a trial rather than simple data on levels of activity, and would also overcome some of the issues participants had with the GENEActiv devices when wearing it repeatedly in the study (notably uncomfortable strap and appearance of the device) which was not widely liked by participants according to outcomes from the focus groups. The ability to use these devices to record and upload the necessary data is possible, and encouraged via developer kits which are specifically targeted at enabling research projects to make use of these devices. This allows the custom software to be written easily, perform as required though the study, with regular uploading of data to a central secure database via data uploads. However, the devices do have the downside of requiring charging regularly (daily) and so further work may be required to both test the software and confirm that participants can be relied on to charge the devices daily. A simple study on participant use of such devices would not be particularly difficult to undertake and would enable data to be collected

about whether the wear patterns of these devices over time would allow the level of data required to be collected.

Utilising all the data collected within this thesis, it appears that a 12- or 18-week study, utilising a blinded, placebo-controlled, parallel arm design, appears both feasible and justified based on the lessons learnt from FaST-MP. The dose range for methylphenidate available to participants should be increased, with a suggested maximum dose of 60mg per day in divided doses. The use of modern wearable technology could be utilised, but would need collaboration with appropriate expertise to ensure the design and function meets the needs of the study and is secure, meeting data protection regulations. The questionnaire outcomes could be reduced significantly; the use of FAS, HADS, SF-12 and KSQ is suggested based on the data collected, and clinical efficacy could be proven with a sample size of just 134, a feasible target across multiple sites even if a minimum duration of disease cut-off were to be specified as part of the eligibility criteria.

8.6 Concluding remarks

Taking an RCT from conception through to completion and analysis within a three-year PhD, even one the size of *FasT-MP*, has been a great challenge. This was made more demanding by issues relating to staffing and facilities encountered through the study. Overcoming such problems and delivering the connected studies presented within this thesis has been a highly educational experience, both with respect to the outcomes that were answered within this thesis, and from the point of view of an individual developing skills relating to clinical trial work. The outcomes from this work provide useful information relating to the feasibility of a future study and it is hoped will influence decisions relating to the design of any trial stemming from this work.

Proceeding to a multi-centre RCT to investigate the clinical efficacy of methylphenidate for sarcoidosis-associated fatigue is not planned in the immediate future, a decision which is driven by two factors. Firstly, the question of fatigue change over time in patients receiving usual care needs to be answered, as well as

the consideration of the potential utility of adopting new wearable technology to produce an improved outcome measure; these questions were not answered within this thesis. Secondly, discussion with other hospitals needs to occur about proceeding to a multi-centre study; although the data from this research suggests that a full-size study is feasible, it requires other centres to commit to participating in this work. In the event that other centres are not keen to support this then a future trial cannot take place.

In conclusion, this thesis and the publications arising from it have demonstrated that performing a study to determine the clinical efficacy of methylphenidate for sarcoidosis-associated fatigue is feasible, but some further development work, coupled with an assessment of organisational capacity, will be required to deliver such a trial. Nevertheless, improving the evidence base for potential interventions for sarcoidosis-associated fatigue remains an important aim and it is hoped that the outcomes from this thesis can help contribute to this.

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Appendices

Appendix 1 – Research ethics approvals for studies

Appendix 2 – MHRA approvals (FaST-MP study)

Appendix 3 – Study PIS Forms

Appendix 4 – Topic guide (Focus groups - FaST-MP study)

Appendix 5 – Non-validated questionnaires

Appendix 1 –Research Ethics approvals for studies

NHS
Health Research Authority
South West - Central Bristol Research Ethics Committee
Whitefriars
Level 3, Block B
Lewin's Mead
Bristol BS1 2NT
Email: nrescommittee.southwest-bristol@nhs.net

23 December 2015

Dr Chris Atkins
NIHR Doctoral Research Fellow
Norwich Medical School
Norwich Medical School
University of East Anglia
Norwich Research Park, Norwich
NR4 7TJ

Dear Dr Atkins

Study title:	**A comparison of two wrist-worn accelerometer devices for the measurement of activity in sarcoidosis patients**
REC reference:	**15/SW/0363**
Protocol number:	**1.3-27.11.15**
IRAS project ID:	**193982**

Thank you for your document submission of 22nd December 2015, responding to the Proportionate Review Sub-Committee's request for changes to the documentation for the above study.

The revised documentation has been reviewed and approved by the sub-committee.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Manager Mrs Naazneen Nathoo , nrescommittee.southwest-bristol@nhs.net. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

A Research Ethics Committee established by the Health Research Authority

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA Approval (England)/ NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe,

they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" above).

Approved documents

The documents reviewed and approved by the Committee are:

Document	*Version*	*Date*
Covering letter on headed paper [Covering letter]	1.0	01 December 2015
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Ins. Certs.]		28 May 2015
IRAS Checklist XML [Checklist_14122015]		14 December 2015
IRAS Checklist XML [Checklist_22122015]		22 December 2015
Letters of invitation to participant [Participant Invitation Letter]	v1.0	29 October 2015
Non-validated questionnaire [Non-validated questionnaire]	1.1	27 November 2015
Participant consent form [Consent Form]	v2.0	22 December 2015
Participant information sheet (PIS) [Patient Information Sheet]	v2.0	22 December 2015
REC Application Form [REC_Form_14122015]		14 December 2015
Research protocol or project proposal [Protocol]	v1.3	27 November 2015
Summary CV for Chief Investigator (CI) [CV - CI]	v1.0	06 November 2015
Summary CV for supervisor (student research) [Prof Wilson - CV]		
Summary, synopsis or diagram (flowchart) of protocol in non technical language [Flow Chart]	v2.0	22 December 2015
Validated questionnaire [Fatigue Assessment Scale]		

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

15/SW/0363	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely

Mr Paul Lewis
Chair

Enclosures: *"After ethical review – guidance for researchers" [SL-AR2]*

Copy to: *Ms Hannah Ings*

Ms Laura Harper, Norfolk and Norwich University Hospitals NHS Foundation Trust

A Research Ethics Committee established by the Health Research Authority

NHS
Health Research Authority
East of England - Cambridge Central Research Ethics Committee
Royal Standard Place
Nottingham
NG1 6FS

21 June 2016

Dr Andrew Wilson
Clinical Senior Lecturer
University of East Anglia
Faculty of Medicine, Health Policy and Practice
University of East Anglia
Norwich
NR4 7TJ

Dear Dr Wilson,

Study title:	**Fatigue in Sarcoidosis - A feasibility study investigating the treatment of fatigue in stable sarcoidosis patients using methylphenidate**
REC reference:	**16/EE/0087**
Protocol number:	**190280**
EudraCT number:	**2016-000342-60**
IRAS project ID:	**190280**

Thank you for your letter of 26 May 2016, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Manager, Rebecca Morledge, NRESCommittee.EastofEngland-CambridgeCentral@nhs.net.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

Clinical trial authorisation must be obtained from the Medicines and Healthcare products Regulatory Agency (MHRA).

The sponsor is asked to provide the Committee with a copy of the notice from the MHRA, either confirming clinical trial authorisation or giving grounds for non-acceptance, as soon as this is available.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites listed in the application, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

The Committee has not yet completed any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. We will write to you again as soon as an SSA application(s) has been reviewed. In the meantime no study procedures should be initiated at non-NHS sites.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Copies of advertisement materials for research participants [Poster (advertisement)]	v1.1	22 January 2016
Covering letter on headed paper [Covering letter]	v1.1	05 February 2015
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Insurance document for C Atkins]		
GP/consultant information sheets or letters [Letter to GP]	v1.1	25 November 2015
GP/consultant information sheets or letters [Letter to GP]	v2.0	05 May 2016
Investigator's brochure / IMP Dossier [Simplified IMP Dossier]	v1.0	11 January 2016
IRAS Checklist XML [Checklist_15022016]		15 February 2016
IRAS Checklist XML [Checklist_26052016]		26 May 2016
IRAS Checklist XML [Checklist_15062016]		15 June 2016
Letter from sponsor		
Letters of invitation to participant [Invitation to participate letter]	v1.0	21 January 2016
Non-validated questionnaire [Safety Questionnaires]	v1.0	27 November 2015
Non-validated questionnaire [Costs questionnaire]	v1.2	22 January 2016
Non-validated questionnaire [Withdrawal Questionnaire]	v1.1	22 January 2016
Other [Application Outcome]		21 January 2015
Other [Copy of Application Form]		21 January 2015
Other [Email from Dr Atkins]		23 February 2016
Other [CV for Dr Atkins]		
Other [Discussion Topic Guide - Focus Groups]	1.1	24 February 2016
Other [Completed Reviewer Form]		
Other [Response to Ethics Committee]	v1.1	26 May 2016
Other [Declaration of understanding]	v1.0	05 May 2016
Other [Focus Group Topic Guide]	v2.1	19 May 2016
Other [Re-reply to ethics]	v1.0	14 June 2016
Other [Declaration of understanding]	v1.1	14 June 2016

Other [MHRA letter]	v1.0	09 March 2016
Participant consent form [Participant consent form]	v2.0	29 April 2016
Participant information sheet (PIS) [PIS (clean)]	v3.3	14 June 2016
Participant information sheet (PIS) [PIS (tracked changes)]	v3.3	14 June 2016
REC Application Form [REC_Form_26052016]		26 May 2016
Research protocol or project proposal [Protocol]	v3.1	26 May 2016
Sample diary card/patient card [Participant inclusion card]	v2.0	29 April 2016
Sample diary card/patient card [Current dose card]	2.0	29 April 2016
Summary CV for Chief Investigator (CI) [CV - Professor Andrew Wilson]		
Summary of product characteristics (SmPC) [Summary of Product Characteristics - Methylphenidate]	-	16 January 2015
Summary, synopsis or diagram (flowchart) of protocol in non technical language [Patient flowchart]	2.0	29 April 2016
Validated questionnaire [STOP-Bang (screening)]	N/A	
Validated questionnaire [FAS]	N/A	
Validated questionnaire [FACIT-F]	v4	16 November 2007
Validated questionnaire [HADS]	9(1.08)	22 January 1994
Validated questionnaire [KSQ]	V8	22 January 2010
Validated questionnaire [EQ5D-5L]	N/A	
Validated questionnaire [SF36]	v1.0	05 February 2016

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

16/EE/0087	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely,

Dr Lydia Drumright
Chair

Email:NRESCommittee.EastofEngland-CambridgeCentral@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Ms Lisa Chalkley, Norfolk and Norwich University Hospitals NHS Foundation Trust*

NHS
Health Research Authority

East of England - Cambridge Central Research Ethics Committee
Royal Standard Place
Nottingham
NG1 6FS

Please note: This is the favourable opinion of the REC only and does not allow the amendment to be implemented at NHS sites in England until the outcome of the HRA assessment has been confirmed.

21 April 2017

Dr Andrew Wilson
Clinical Senior Lecturer
University of East Anglia
Faculty of Medicine, Health Policy and Practice
University of East Anglia
Norwich
NR4 7TJ

Dear Dr Wilson

Study title:	**Fatigue in Sarcoidosis - A feasibility study investigating the treatment of fatigue in stable sarcoidosis patients using methylphenidate**
REC reference:	**16/EE/0087**
Protocol number:	**190280**
EudraCT number:	**2016-000342-60**
Amendment number:	**Substantial Amendment 2017/02/24**
Amendment date:	**24 February 2017**
IRAS project ID:	**190280**

The above amendment was reviewed on 07 April 2017 by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Covering letter on headed paper		20 March 2017
Non-validated questionnaire [Exit questionnaire]	1.1	06 March 2017
Notice of Substantial Amendment (CTIMP)	Substantial Amendment 2017/02/24	24 February 2017
Other [Statement of Activities]		
Other [Schedule of Events]		
Other [Flowchart Clean]	2.1	24 February 2017
Other [Flowchart Track Changes]	2.1	24 February 2017
Other [Summary of Amendments]		
Participant consent form [Informed Consent Form]	2.2	24 February 2017
Participant consent form [Informed Consent Track Changes]	2.2	24 February 2017
Participant information sheet (PIS) [Clean]	3.4	24 February 2017
Participant information sheet (PIS) [Track Changes]	3.4	24 February 2017
Research protocol or project proposal [Clean]	3.2	24 February 2017
Research protocol or project proposal [Track Changes]	3.2	24 February 2017
Validated questionnaire [PSQI]		

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

Working with NHS Care Organisations

Sponsors should ensure that they notify the R&D office for the relevant NHS care organisation of this amendment in line with the terms detailed in the categorisation email issued by the lead nation for the study.

Statement of compliance

This Committee is recognised by the United Kingdom Ethics Committee Authority under the Medicines for Human Use (Clinical Trials) Regulations 2004, and is authorised to carry out the ethical review of clinical trials of investigational medicinal products.

The Committee is fully compliant with the Regulations as they relate to ethics committees and the conditions and principles of good clinical practice.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our Research Ethics Committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

16/EE/0087:	**Please quote this number on all correspondence**

Yours sincerely

P.P

Revd Dr Derek Fraser
Chair

E-mail: NRESCommittee.EastofEngland-CambridgeCentral@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Ms Lisa Chalkley, Norfolk and Norwich University Hospitals NHS Foundation Trust*

Health Research Authority

London - Chelsea Research Ethics Committee
Research Ethics Committee (REC) Bristol Centre
Level 3, Block B
Whitefriars
Lewins Mead
Bristol
BS1 2NT
Telephone: 020 7104 8052

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

07 November 2017

Dr Chris Atkins
Norwich Medical School
Bob Champion Research and Education Building
University of East Anglia, Norwich
NR4 7UQ

Dear Dr Atkins

Study title:	**A comparison of health status scores in patients with sarcoidosis**
REC reference:	**17/LO/1872**
Protocol number:	**1.2**
IRAS project ID:	233583

Thank you for your letter of 1st November 2017, responding to the Proportionate Review Sub-Committee's request for changes to the documentation for the above study.

The revised documentation has been reviewed and approved by the sub-committee.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact please contact hra.studyregistration@nhs.net outlining the reasons for your request.

Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

The Committee noted that the PIS is too concise, for example the section regarding Sarcoidosis, and requested that the PIS is revised in lay language

You confirmed that the amended PIS document has been changed to reflect the comments from the sub-committee. The document is now longer to include additional information regarding sarcoidosis, and has been re-written in appropriate lay language. To ensure that the changes are acceptable, I have asked two patients with sarcoidosis to review the document – both suggested minor changes that have been incorporated in order to simplify some of the language; both are happy with the final version, which is submitted here.

The Committee accepted this response

You should notify the REC once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. Revised documents should be submitted to the REC electronically from IRAS. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which you can make available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA Approval (England)/ NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" above).

Approved documents

The documents reviewed and approved by the Committee are:

Document	*Version*	*Date*
Covering letter on headed paper [Covering letter]	v1.0	09 October 2017
Covering letter on headed paper [Covering letter]	v1.0	01 November 2017
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Insurance and Indemnity Letter - UEA]		12 October 2017
IRAS Application Form [IRAS_Form_12102017]		12 October 2017
IRAS Application Form XML file [IRAS_Form_12102017]		12 October 2017
IRAS Checklist XML [Checklist_01112017]		01 November 2017
Letters of invitation to participant [Letter of invitation]	1.1	07 August 2017
Non-validated questionnaire [Background/Demographic	1.1	08 August 2017

information Questionnaire]		
Participant information sheet (PIS) [PIS]	v1.5	01 November 2017
Participant information sheet (PIS) [PIS (changes tracked)]	v1.5	01 November 2017
Research protocol or project proposal [Protocol]	v1.2	02 October 2017
Summary CV for Chief Investigator (CI) [CI - CV]	N/A	
Summary CV for student [CV (student)]		26 September 2017
Summary CV for supervisor (student research) [CV - Andrew Wilson]		
Validated questionnaire [Kings Sarcoidosis Questionnaire]	V8	26 September 2010
Validated questionnaire [Short Form 36]	v1.0	05 February 2016
Validated questionnaire [EuroQoL-5D-5L]	N/A	26 September 2009
Validated questionnaire [Fatigue assessment scale]	anonymised	
Validated questionnaire [Hospital Anxiety and Depression Scale]	anonymised	

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance

We are pleased to welcome researchers and R & D staff at our RES Committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

17/LO/1872	Please quote this number on all correspondence

With the Committee's best wishes for the success of this project.

Yours sincerely
PP

Dr Michael Schachter
Chair

Email: nrescommittee.london-chelsea@nhs.net

Enclosures: *"After ethical review – guidance for researchers" [SL-AR2]*

Copy to: *Ms Sarah Green*

Ms Laura Harper, Norfolk and Norwich University Hospitals NHS Foundation Trust

Appendix 2 – MHRA approval (FaST-MP)

MHRA
151 Buckingham Palace Road
London SW1W 9SZ
United Kingdom

mhra.gov.uk

Dr C Atkins
UNIVERSITY OF EAST ANGLIA
NORWICH MEDICAL SCHOOL
CHANCELLOR'S DRIVE
NORWICH
NR4 7TJ
UNITED KINGDOM

26/08/2016

Dear Dr C Atkins

THE MEDICINES FOR HUMAN USE (CLINICAL TRIALS) REGULATIONS 2004 S.I. 2004/1031

Our Reference:	22238/0001/001-0002
Eudract Number:	2016-000342-60
Product:	Methylphenidate 10mg tablets
Protocol number:	190280
Substantial Amendment Code Number:	Code Number: 190280
Version: 3.1	
Date: 2016/05/26	

NOTICE OF ACCEPTANCE OF AMENDMENT

I am writing to inform you that the Licensing Authority accepts the proposed amendment to your clinical trial authorisation (CTA), received on 05/08/2016.

This amendment may therefore be made.

You are reminded that where it is appropriate, the Ethics Committee should also be notified of amendments.

Yours sincerely,

Clinical Trials Unit
MHRA

Medicines and Healthcare Products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

MHRA
151 Buckingham Palace Road
London SW1W 9SZ
United Kingdom

mhra.gov.uk

Dr C Atkins
UNIVERSITY OF EAST ANGLIA
NORWICH MEDICAL SCHOOL
CHANCELLOR'S DRIVE
NORWICH
NR4 7TJ
UNITED KINGDOM

23/05/2017

Dear Dr C Atkins

THE MEDICINES FOR HUMAN USE (CLINICAL TRIALS) REGULATIONS 2004 S.I. 2004/1031

Our Reference:	22238/0001/001-0003
Eudract Number:	2016-000342-60
Product:	Methylphenidate 10mg tablets
Protocol number:	190280
Substantial Amendment Code Number:	NA

NOTICE OF ACCEPTANCE OF AMENDMENT

I am writing to inform you that the Licensing Authority accepts the proposed amendment to your clinical trial authorisation (CTA), received on 21/04/2017.

This amendment may therefore be made.

You are reminded that where it is appropriate, the Ethics Committee should also be notified of amendments.

Yours sincerely,

Clinical Trials Unit
MHRA

Medicines and Healthcare
Products Regulatory Agency

Appendix 3 – PIS forms

Prof A M Wilson

Department of Respiratory Medicine

Norfolk & Norwich University Hospital

Colney Lane

Norwich

NR47UY

Website: nnuh.nhs.uk

Direct Dial: 01603 298639

Direct Fax: 01603 289640

Information about Respiratory Research – Participant Information Sheet

Study Title – A comparison of two wrist-worn accelerometer devices for the measurement of activity in sarcoidosis patients

Short title - Comparison of accelerometers for the measurement of daily activity

We would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. Talk to others about the study if you wish. Part 1 tells you the purpose of this study and what will happen to you if you take part. Part 2 gives you more detailed information about the conduct of the study. Please ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

PART 1

What is the purpose of the study?

This study is comparing two wrist-worn accelerometer devices. The devices measure how active a person is over the period of a week. We intend to use devices like these in the future in a number of trials. In order to decide which the best to use is we need to test them head-to-head with patients. This will allow us to see which devices patients think are the best, as well as whether they are able to collect the data that we need as researchers.

Why have I been invited?
You have been diagnosed with a condition called sarcoidosis.

Do I have to take part?
No. The decision to participate is entirely up to you. We will describe the study here, and if you have further questions then you are welcome to contact us. If you are interested in taking part after reading this information sheet, then please fill in the consent form and return it to us. If you are not interested, it will not influence in any way your future treatment from us.

What will happen to me if I take part?
If you agree to take part then we will first ask you to sign a consent form to indicate your willingness to take part. Once you have signed to indicate that you are willing to participate in the trial you will be asked to fill in a short questionnaire (10 questions) which will tell us about any tiredness or fatigue you may be feeling, then one of the research team will show you the two devices (which are each like a small wrist-watch) and ask you to wear them on your non-dominant wrist (i.e. your left wrist if you are right-handed). You will need to continue wearing the device for 7 days, and you will need to wear them for 24 hours per day. You will be able to shower as the devices are waterproof. However, one of the devices (which has a Velcro strap) should be removed if you go swimming or have a bath. The black plastic device can remain on your wrist 24 hours a day throughout the 7 day period.

The devices will be active for the 7 day period. Once the device has been worn for seven days you can take them off. We will provide you with a pre-paid envelope to return them to us by post. We will also give you a questionnaire to answer for each of the devices to gain your opinion on how comfortable the device is to wear and any problems you may have had with them. These questionnaires should be returned in the freepost envelope with the accelerometer devices.

Because the position that you wear the devices may affect the results collected (i.e. one device will be closer to the wrist/hand than the other as both devices are worn on the same arm), we will ask you to wear the devices in a specific order. You will be told which device you will need to wear closest to your wrist over the 7 day period.

We will not be testing any drug during this study, nor will you be asked to change any of your usual medications.

Expenses and payments
You will be reimbursed for your travel expenses, including validation of your car parking if you park in the main car park.

What will I have to do?
We will ask you to fill in one questionnaire when you are first seen. Following this, we ask that you wear two wrist-worn accelerometers on your non-dominant wrist for 7 days (wearing it for 24 hours each day). At the end of the 7 day period you can take the devices off, and we ask that you fill in a questionnaire for each of the devices (with regards to how acceptable you found the devices and whether you

had any problems with them). After this, we would like you to return the devices and the questionnaires to us in the pre-paid envelope that we will provide.

What are the possible disadvantages and risks of taking part?
There are no risks associated with wearing the device, apart from the fact that you have to wear it. As you are wearing two devices at the same time on the same wrist there is the possibility that they will become uncomfortable. The reason for wearing them simultaneously on the same wrist is so we can directly compare the data that we get from each device. This will help us decide which device will be best for meeting our needs in future studies.

What are the potential benefits of taking part?
Wearing the accelerometers and giving us your opinion on the devices will help to choose which of them we will use in the future, therefore you will be helping us to ensure that we are using the best possible equipment for future studies.

What happens when the research study stops?
After the motion devices have been returned to us with the questionnaire you will not be asked to do anything further. The results will be analysed and help us to decide which of the two devices to use in the future.

What happens if there is a problem?
Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in Part 2.

Will my taking part in the study be kept confidential?
Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2.

PART 2

What will happen if I don't want to carry on with the study?
You can withdraw your consent at any time. This will not have any effect on your care from this department if you do decide not to continue your participation. Once your motion device is returned, the results will be entered into our system and cannot be removed, so you will be unable to ask for your answers to not be included in the final results once this has been done.

What if there is a problem?
We do not envisage that you will suffer any problems or harms from taking part in this study. However, If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions (01603 289876). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure (or Private Institution). Details can be obtained from Patient Advice and Liaison Service (PALS) 01603 289036.

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against University of East Anglia or Norfolk and Norwich University Hospitals NHS Foundation Trust but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate).

Will my taking part in this study be kept confidential?
Yes. None of the data from the accelerometer devices or your questionnaires will have your name directly linked to them. They will all be identified by a unique reference number. A document linking your name with this unique reference number will be kept in a on a password protected file on a secure computer server and in a secure office. The only people having access to this information will be the researchers conducting the study. The researchers will need to link your questionnaires back to your clinical records.

Will my GP be involved?
We will not contact your GP routinely to inform them that you have decided to take part in the study, though we will ask your consent to inform your GP of your participation should it become necessary. We will only contact your GP if you agree to this.

What will happen to the results of the research study?
The results will be analysed in two parts. The first part will involve analysing the results of the questionnaires you provide. This will tell us what the participants in the study thought of the devices, and which one was preferred. The second part involves analysing the data from the devices. This will tell us how reliable the devices are, and whether they collect the data that we need. These results will influence the choice of devices for any future trials which will involve the use of accelerometers.

Who is organising the research?
The research is being organised by researchers from Norwich Medical School, University of East Anglia and Norfolk and Norwich University Hospitals Foundation Trust. None of the researchers will receive any payment or funding for including you in the study. The study forms part of a PhD for Dr Atkins which has been funded by a doctoral research fellowship from the National Institute of Health Research (grant number DRF-190-08-2015)

Who has reviewed the study?
All research in the NHS is looked at by independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity.

Further information
You can receive general information about participating in research from your doctor or from the Public and Patient Involvement in Research (PPIRes) phone 01603 257292 http://www.nnuh.nhs.uk/Dept.asp?ID=265. Your doctor or the researchers will be able to answer any specific questions about this study and whether you should participate. If you are unhappy with the study please contact Dr Atkins on 01603 298876 or on PALS 01603 289036.

Thank you for your consideration of taking part in this study. If you are still interested, or have any further questions, then please contact the study team using the details below:

Dr Chris Atkins
Phone 01603 289876

Respiratory.research@nnuh.nhs.uk
Department of Respiratory Medicine, Norfolk and Norwich University Hospital, Colney Lane, Norwich, NR4 7UY

University of East Anglia

Norfolk and Norwich University Hospitals NHS
NHS Foundation Trust

Information about Respiratory Research – Participant Information Sheet

Fatigue in Sarcoidosis – A feasibility study investigating the treatment of fatigue in stable sarcoidosis patients using methylphenidate

Short title **- Fatigue in Sarcoidosis - Treatment with Methylphenidate**

We would like to invite you to take part in our research study. Before you decide if you would like to take part, we would like to explain why the research is being done and what it would involve for you. If you are interested, one of our researchers will go through this information with you and answer any questions you may have.

Please take time to read the following information carefully. Talk to others about the study if you wish. Please ask us if there is anything that is not clear or if you would like more information.

This information sheet is divided into three parts:

- Part 1A describes why we are doing the study, what it would involve for you, and what the main benefits and risks are.
- Part 1B describes in more detail the focus groups (discussion groups) which will occur after the main study is completed, and is an optional part of the overall study.
- If you are interested in taking part please read part 2 which contains further important information.

Thank you for taking the time to read this leaflet.

Part 1A

What is the purpose of this research study?

Sarcoidosis is a condition, of no known cause, which can cause symptoms involving many parts of the body including the lungs, skin and joints. Fatigue or troublesome tiredness – which means the feeling of tiredness which is not relieved by rest or sleep - is also a common problem in sarcoidosis and is a challenge for doctors looking after patients with this condition because it often persists even when the other symptoms have been treated. We would like to investigate whether a medicine (called methylphenidate), which has been used for many years to help people with other conditions, can improve the fatigue associated with sarcoidosis. At present we do not have enough information or evidence to recommend that it is widely used. We would therefore like to carry out a large clinical trial in the future to confirm whether or not methylphenidate improves fatigue in sarcoidosis. However, before we can do this we need to do a smaller study involving up to 30 patients to see if this would be possible.

The study will compare methylphenidate versus a placebo (a dummy sugar capsule). Both of the capsules look identical and neither you, nor the researchers, will know which medication you have taken until the end of the study. This is of vital importance to ensure that the study remains fair. The results could be spoilt if anyone found out which capsule you were taking before the study is over. The decision about whether you receive methylphenidate or the placebo is made randomly by a computer. You will be asked to take the medication twice a day for up to 6 months. You will start on one capsule twice a day, and will increase to two capsules twice a day after being reviewed by the research team.

This feasibility study will find out if patients are willing to take a drug like methylphenidate every day, how many patients are suitable to receive the drug, and how likely it is that patients who enter the trial will complete it. We will monitor you throughout the trial, ask you to complete questionnaires about how bad your fatigue is, what your quality of life is like, what your mood is like, and ask you to perform some tests that measure how well your lungs are working, how much exercise you can do, and how active you are. In addition, if you are willing, we would like you to ask to come to a meeting after the trial to discuss your experience whilst taking part. These will all be explained in more detail later in this information sheet.

Why have I been invited?

You have been invited because you have sarcoidosis and might suffer with significant fatigue.

Do I have to take part?

No. The decision to take part is entirely up to you. We will describe the study here and go through this information sheet with you.

What will happen to me if I take part?

This study involves up to 8 visits, plus one optional final visit to discuss your experience in the trial with a group of other participants in the trial once you've completed all the visits. These visits will all take place at the Norfolk and Norwich Hospital. The visits will all be in addition to the usual care that you receive. In addition, you will be called by the research team between visits to see how you are getting on with the medication and whether you are having any problems. The study will involve taking the trial medication every day in the morning and afternoon for up to 24 weeks.

You will be asked to attend the following visits:

Screening Visit: This first visit is our opportunity to explain the study in detail and answer any questions you may have. We will ask you to complete a consent form and ask a number of questions to make sure that there is nothing that would prevent you from taking part in the trial. We will also check your current medications to make sure that you are receiving no medications that would interfere with the study drug. We will ask you to complete some questionnaires to measure your fatigue before starting any medications, and to look for any problems with your sleep that may need treatment separately. We will take some blood tests and perform a heart wave test called an electrocardiogram (ECG); these tests will ensure that it is safe for you to take the medication. We will ask you to perform a walking test and to wear a device that looks like a wrist-watch for 7 days so we can measure how active you are. You can post the device back to us or bring it with you at your next visit. Finally, we will ask you to perform a breathing test where you will need to forcefully blow into a tube (you may have performed this test in clinic). In total this visit will take between 60 and 90 minutes.

Baseline visit after 2 weeks: We will check that it is still safe for you to continue with the research. We will ask you to fill in eight questionnaires. These will measure your quality of life, your mood, your sleep quality, whether there is any evidence of your sarcoidosis causing you problems, and measure your fatigue levels. We will also ask you to complete a questionnaire about whether your fatigue and your underlying condition is costing you money and leaving you out-of-pocket. Finally, if you did not perform a walking test when you were seen at the screening visit then it will be performed at this visit. Once all this has been completed we will give you a supply of medication that will last you until your next visit after 2 weeks. This visit will take approximately 60 minutes.

Follow-up visits: We will arrange to see you at the hospital after 2, 4, 6, 12, 18 and 24 weeks. During these visits we will check to make sure that it is still safe for you to take the medication and that you are still willing to be involved. If so, we will ask you about potential side effects that you may be noticing from the medication, ask you to fill in the same questionnaires as before regarding your fatigue, general well-being, quality of life, mood and costs that you may have suffered because of your condition. Whilst you are receiving the medication we will take some blood tests and perform a heart wave test. At the beginning of the trial (before you start treatment), at 12 weeks into the trial and after 24 weeks (at the final visit) we will also ask you to perform the breathing tests, walking tests and to wear a device on your wrist to

measure your activity levels. At your final visit we will also briefly ask you to answer some questions about your thoughts on the trial and the medication you received.

At each visit we will give you a supply of medication to see you through to your next visit. The number of questionnaires and tests at each visit varies and so the length of each visit will be different but will be between 30 and 90 minutes depending on what is being checked at each visit; an estimate of how long each will be is shown at the bottom of the table below.

After the study: At your final visit, if you are taking the higher dose of medication (two capsules twice daily) then we will give you a two week supply of medication at the lower dose of one capsule twice daily to gradually discontinue the drug. We will also send you a final pack of questionnaires in the post to complete; this will occur approximately six weeks after you attended your last visit, and the questionnaires can be returned to us by post.

In addition to these visits in hospital, we will telephone you between visits to see how you are and ensure that you are not developing any side effects. We will telephone you each week between study visits up until your six week appointment. After this, we will phone you every two weeks between visits to see how you are getting on with the medications. Each phone call will last between 5 and 10 minutes and will be conducted by a member of the trial team. All members of the team who will contact you will have been appropriately trained to ask about any potential side effects, will be employed by the NHS (not by the university or other external bodies) and have a duty of confidentiality to you regarding anything discussed on the phone. If any problems are flagged up during these phone calls then you will have the opportunity to speak to one of the doctors running this study.

To help you understand the steps involved in the study and the measurements taken at each visit, please see the table below showing which measurements are taken at which visit:

	Visit Time point								
Procedure / Assessment	Screening visit	0 weeks	*2 weeks*	*4 weeks*	*6 weeks*	*12 weeks*	*18 weeks*	*End of trial (24 weeks)*	*6 weeks post-trial*
Informed consent taken	✓								
Entry criteria checked	✓								
Blood tests	✓		✓	✓	✓	✓			
Pregnancy Test (females)	✓	✓							
Heart tracing	✓		✓	✓	✓	✓		✓	
Treatment dispensed		✓	✓	✓	✓	✓	✓		
Questionnaires	✓	✓	✓	✓	✓	✓	✓	✓	✓ (post)
Breathing tests		✓				✓		✓	
Walking test		✓				✓		✓	
Wrist-worn device to measure activity (7 days)	✓					✓		✓	
Side effects monitoring			✓	✓	✓	✓	✓	✓	
Time in minutes for each visit (approximately)	**60-90**	**60**	**30-45**	**30-45**	**60**	**60-90**	**30**	**60-90**	**n/a**

Finally, there is an optional group visit at the end of the study that we will ask your consent to invite you to attend. This is to discuss the experience of patients who participated in the trial and to see whether there were any problems occurring that we hadn't anticipated. This is an optional extra part of the trial and it is not mandatory for you to attend if you wish to take part in this study. We will ask you to indicate on the consent form whether you would be happy for us to invite you to participate in this after you have completed the medication. This part of the study is described in more detail in section 1B of this information sheet.

What are my responsibilities?

You will need to bring a list of your current medications that you are currently taking to each visit, including the first visit (screening visit). If you are taking any medications, either prescribed from your doctor or over the counter, it is important that you let the trial team know about them. You will also need to bring all trial medication bottles you have been given (whether empty or not) to each visit. We will ask you about any potential side-effects at each visit. We need to know if you develop any potential side effects – if you develop problems on the drug then we would be most grateful if you could let us know using the research contact details below.

It is also important that when you are taking the medication you do not take any over-the-counter flu remedies or nasal decongestants. These drugs interfere with methylphenidate and can cause your blood pressure to become very high.

Methylphenidate itself can cause the sensation of a blocked nose or nasal stuffiness so it is important to be aware not to take medications like otrivine, night nurse or flu-relief. Simple paracetamol or ibuprofen is fine. More information about side effects is displayed below.

We do not know if methylphenidate is safe during pregnancy or whilst breast feeding; for this reason we are unable to include patients who are pregnant or breast feeding into the trial. For females in the trial, if you have not gone through the menopause and may be able to become pregnant during the trial it is important that you use adequate contraception. During the trial, adequate contraception consists of using two methods of contraception when having sex – this means a hormonal contraception (this would be a contraceptive pill, an injection or an implant), a coil (such as the mirena coil), or a barrier method (this would be a condom or diaphragm/cap with spermicide). Alternatively, complete abstinence from sexual activity whilst participating in the trial is acceptable. If you were to become pregnant during the trial you must let the trial team know as soon as possible.

What are the potential side-effects of methylphenidate?

In this study there is a 60% chance that you will receive methylphenidate; out of every five people enrolled in the trial, three of them will receive methylphenidate. All medications have potential side effects. It is important that you are aware of the potential side-effects of methylphenidate before you take part in the study. You will also have received a copy of the information sheet about methylphenidate (called a *Summary of Product Characteristics*) with this information sheet so you can read more about the drug if you wish to.

The side-effects are broken down into the frequency with which they occur:
Very Common (more than 1 in 10 frequency): Insomnia (difficulty getting to or staying asleep), nervousness, headache.

Common (between 1 in 10 and 1 in 100 frequency): Inflammation or irritation of the nose (blocked nose), decreased appetite, change in moods, irritability or aggression, low mood/depression, dizziness, abnormal movements, restlessness, sleepiness, irregular heart beats, fast heart beats, palpitations (awareness of your heart beat), high blood pressure, cough, sore throat, stomach pains, diarrhoea, nausea, vomiting, dry mouth, hair loss, high temperatures, rashes, weight loss.

Uncommon (between 1 in 100 and 1 in 1000 frequency): Allergic reactions to the medication (causing wheals or swelling of the lips, face or ears), other skin conditions and rashes, psychosis (bizarre behaviour), hallucinations (seeing, hearing or feeling things that aren't there), anger, suicidal ideation, altered mood and mood swings, tearfulness, tics (repetitive movements), tremor, double vision, blurred vision, chest pains, shortness of breath, constipation, abnormal liver tests on blood results, muscle aches and pains, blood in the urine, tiredness, heart murmurs.

Rare (between 1 in 1000 and 1 in 10,000 frequency): Mania (extremely high mood with associated strange or unusual behaviour), disorientation, libido disorder (loss of sexual drive or increased sexual drive), difficulties adjusting vision to distance or

light, dilated pupils, angina, increased sweating, gynaecomastia (increase in breast tissue).

Very Rare (less than 1 in 10,000 frequency): Low blood counts, suicide attempts, abnormal thinking, apathy (loss of drive to do anything), repetitive behaviours, convulsions and seizures, stroke, dangerously high temperature and muscle damage (referred to as *Neuroleptic Malignant Syndrome)*, heart attack, cardiac arrest, peripheral coldness and abnormal reaction of the hands and feet to cold situations.

We will contact you at least every two weeks during the study so that we can check the study medication is not causing you any problems but if you are worried about anything in between then please contact us on either 01603 289876 or 01603 289633 (Monday to Friday, 9am to 5pm).

Is methylphenidate addictive?

Methylphenidate is a stimulant medication, and is similar to some other medications such as amphetamines. The dose that we are using in this trial is small and there should not be a risk of addiction if the medication is taken as directed by the research team. It has been used at this dose in other trials and has not caused problems with addiction. However, if the medication is taken at a much higher dose than directed then it can be addictive and the risk of side effects goes up. *It is dangerous to take more than the dose prescribed by the research team*

Methylphenidate is a controlled drug. This means it is illegal to give your medications to anyone else. We will ask you to sign a short form when signing your consent to indicate your understanding that you must only take the medication as directed by the trial team, and never give away your medication to anyone else.

Are there other medications that I am prescribed that could affect the safety of the trial medication?

There are a number of medications that should be avoided in combination with methylphenidate. This is because they increase the chance of developing side effects from methylphenidate. Because we do not know whether you will be receiving methylphenidate or not we need to assume you are receiving the drug. We will carefully check with you at the first visit and at each follow-up visit to see if you are taking any of the medications that could interact with methylphenidate. Some medications can be changed for suitable alternatives and would mean you can take part in the research. This would only happen if you are willing to receive an alternative medication and if your GP or hospital consultant is willing to prescribe this.

We will carefully check your list of medications each time we review you as part of the study, but if you are prescribed or taking any of the medications from the following list then you need to let the researchers know as soon as possible and stop taking the trial medication:

- **Tricyclic anti-depressants** (e.g. amitriptyline, clomipramine, dosulepin, doxepin, imipramine, lofepramine, nortriptyline, trimipramine, mianserin, trazodone)
- **Monoamine oxidase inhibitors** (e.g. phenelzine, isocarboxazid, tranylcypromine, moclobemide, selegiline)
- **Antipsychotic medications** (e.g. Haloperidol, Risperidone, Clozapine, Amisulpride, Olanzapine, Paliperidone, Quetiapine)
- Buprenorphine, Tramadol
- Levodopa
- Clonidine
- Methylene blue
- Warfarin (there is a risk that control of your blood's clotting level will be unsafe whilst on methylphenidate)
- **Decongestants and cold/flu relief medications** (phenylephrine, ephedrine, pseudoephedrine and others). Steroid nasal sprays are allowed

Please check with the trial team before starting any new medications if you are unsure.

I'm being asked to wear a device on my wrist at times during the study – what do I have to do and what is this for?

At three times during the study (before you start the medication, half way through the trial and just before you stop the medication) you will be asked to wear a device called an accelerometer on your non-dominant wrist for a seven day period. This is the size and shape of a wrist-watch but it measures movement, and from this we can estimate how active you are. It can also make some simple measures of the quality of your sleep. The device is fully waterproof and can be worn 24 hours a day, including in the shower, the bath or when swimming. Some people don't like to wear anything on their wrist when in bed, and if this is the case you can remove the device overnight. We would like you to wear the device as much as possible and for at least 10 hours a day for each of the 7 days whilst you are asked to wear it.

What are the possible benefits of taking part?

There are no direct benefits to taking part.

What are the possible disadvantages of taking part?

There are a lot of visits to attend and one disadvantage is the time required for you to travel to the hospital and have these follow-up visits. This can incur expenses, and so we will reimburse your travel costs; we will reimburse your travel & parking expenses at the current accepted rate if travelling by car, or bus/train/taxi fares against receipts if using public transport. You may suffer some discomfort from the blood tests performed. You may also experience some side effects from the study medication (see above). Before participating you should consider whether this will affect any insurance you have and seek advice if necessary.

What happens when the research study ends?

When you have completed the study medications and completed the questionnaires sent to you, this signifies the end of your involvement in this research study. You will not receive any further trial medications after you have completed the 24 weeks of treatment (plus a further two weeks of a lower dose if you completed the study on the higher dose). **You will not be able to continue receiving methylphenidate once the trial is over.**

When the research is finished we will send a summary of the results to anyone who was involved in the trial, or who indicated an interest in the trial but was unable to participate. At the end of the study, if you would like to know which treatment you received (methylphenidate or placebo) then please contact us (see 'researcher contacts' below).

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Part 1B

What is a "Focus Group"?

A focus group is a form of research where people are asked about their opinions and perceptions. Questions are asked in a group setting where participants are free to talk and discuss with other group members.

What is the purpose of these focus groups?

The main trial that you have been asked to participate in is being performed to find out whether it is possible to design a large clinical trial in the future to confirm whether or not methylphenidate improves fatigue in sarcoidosis. As part of this it is very important that participants in the trial have the opportunity to discuss their experiences. This allows the research team to hear what went well and what didn't go well with the trial from your perspective. These discussions may help to improve the design of future trials for patients like yourself.

Do I have to take part?

No. The focus group participation is optional, and the decision to take part is entirely up to you. If you decide that you would rather not participate in the focus group meeting at the end of your time in the study then you can still take part in the main study. If you decide at this point that you *would* like to take part in the focus groups at the end of the study and then later decide that you would rather not then that is also fine – you can withdraw your consent at any time for this part of the study without withdrawing from the entire trial. If you sign the consent form to indicate that you are happy to take part in the focus groups, we will approach you after the end of the trial to make sure that you're still happy to come to one of the group meetings at a time that is convenient for you.

What will happen to me if I take part in these focus groups?

The focus group sessions occur after you have finished the trial. We hope that they will occur about 6-8 weeks after you finish taking the study medication but it could be a bit sooner or later depending on how many people are finishing the trial at the same time as you (everyone will start and finish at different times).

If you come to one of the focus groups then it will take place at the Norfolk and Norwich University Hospital. We will contact you at least 2 weeks in advance of any meeting to try and arrange a meeting time which is suitable for everyone. At this point we will confirm where the meeting would be and send directions to the meeting to you in the post (as well as confirmation of the time and date). You do not need to do or prepare anything in advance.

On the day of the focus group meeting, when you come to the meeting there will be at least one member of the research team there to act as a moderator and to help facilitate discussion – it is also an opportunity for you to ask any questions of the research team that you may have. There will be up to 6 other participants in the group. There will be refreshments provided. **You are welcome to bring a friend,**

partner or spouse with you when you come but they will not be able to take part in the group discussion.

When everyone has arrived then the representative of the research team will open the discussion, initially welcoming everyone and then discussing the ground rules for the session. After this, the discussion will focus around two main aspects:

1. Experiences of the trial (e.g. Best and worst things about taking part, any part of the trial that put you off taking part or that was particularly problematic?)
2. Changes to the trial (e.g. Would you change anything about the trial if you could?)

During the session the conversation is taped. This is to allow all the discussion to be recorded without having to take lots of notes at the time.

There will be a break in the middle of the session. After these topics have been discussed, and the member of the research team present has summarised and made sure that no significant points have been missed, then you will be free to go. You will not be required to attend any further groups or sessions. In total, we expect a focus group session to last between 60 and 90 minutes, although it may run on a bit longer (but not more than 2 hours).

What happens when the focus group ends?

When the focus groups have been performed then the study will be over. You will not be asked to attend any further groups and there will be no further commitment from you. In total we hope to perform three focus groups of 6 people each but you will only be asked to attend one of these meetings. To find out what we do with the data generated during the focus groups, please see the section, “”What will happen to the results of these focus groups” below.

Will the points I raise in discussion be confidential?

Any comments you make in the focus groups are not attributed to you when they are reviewed, so feel free to say what you really think! There will be other patients at the focus group contributing to the discussion, so the people attending the meeting will be able to hear your points of view, but we ask that everyone’s views are respected at the meetings.

I am not taking part in the *“Fatigue in Sarcoidosis – Treatment with Methylphenidate”* study. Can I still take part in these group discussions?

Unfortunately not. We are interested in the views of participants who have undertaken the trial. If you were unable to take part in the main trial then we are unable to invite you to participate in the focus groups.

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Part 2

What happens if new information becomes available?

Sometimes we get new information about the study treatment. If this happens then we will tell you about the new information that has become available and discuss what this means for you. If new information becomes available that affects whether or not this study can continue we will inform you, your General Practitioner and your respiratory consultant at the earliest opportunity.

If, once you have had time to think about what you have been told, you decide not to carry on in the study, your routine care will continue as normal. If you decide to continue in the study you may be asked to sign an updated consent form.

What will happen if I don't want to carry on with the study?

You can withdraw your consent to participate at any time without having to give a reason. This will not have any effect on the care you receive if you do decide not to continue your participation. We will need to use the data collected up until your withdrawal. If you do not wish to continue taking the study medication we will invite you to continue attending follow-up visits until you would have expected to end the trial, including the questionnaires, breathings tests, walking tests and activity measurement. If you choose to withdraw from the study we would be very grateful if you could complete a short questionnaire on your reasons. It is entirely up to you if you choose to complete this questionnaire. The answers are confidential and do not influence your clinical care in any way.

What happens if there is a problem?

If there is a particular issue that you would like to discuss with the researchers then please use the contact details below (see 'contact for further information'). For any complaint about the way you have been dealt with during the study then please address this with either the researchers or the Patient Advice and Liaison Service (PALS) on 01603 289036.

What provisions are in place for compensation if required?

The NHS indemnity scheme applies if you were to come to harm as a result of the management, design or conduct of the research where legal liability rests with the investigator or sponsor. If you are harmed during the research due to someone's negligence then you may have grounds for legal action for compensation against your hospital, but you may have to pay your legal costs.

What safeguards are in place?

We will monitor blood tests and the test of your heart's electrical activity (the ECG) closely at regular points during the trial. You will also be in regular contact with the trial team who will ask you about any potential side effects that you may be experiencing, to try and identify problems at the earliest opportunity.

If you are concerned about a possible side-effect of the treatment or have any concerns about the study then you can contact the trial team using the details below. Alternatively you may wish to consider getting medical advice via your General Practitioner or Accident and Emergency if you have a serious problem.

Can I claim travel expenses?

We will reimburse both the transport costs for the return journey from your home to the Norfolk and Norwich University Hospital and will validate the ticket for the hospital car park (if you come by car) during the clinical trial visits*. Please note that we are unable to validate car parking tickets if you park in the private car park opposite the hospital – this is opposite the helipad and next to the University building.*

Will my taking part in the study be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled with the strictest confidence. All information which is collected about you during the research will be held securely in accordance with the Data Protection Act. It will be kept for 5 years after which it will be disposed of securely. All of your data (your questionnaire information, samples and clinical details) will be labelled by a code and will not have your name or any other details about you on it. We refer to this as linked anonymised as although your test results are anonymous, it can be linked to you by a code. The code will only be known by the members of the research team. It will be kept securely. All the members of the research team who you will have contact with, either at a visit where you come to the hospital or where you are contacted by the team over the phone, will work for the NHS, not the university or other external agencies. They will have the same duty of confidentiality to you as any other member of your medical team who you would see for treatment of your condition.

Researchers at Norwich are conducting the statistical analysis of the study, and to maintain confidentiality, the statistical team will only analyse completely anonymous data. Any reports or publications arising from the study will contain totally anonymised data so that it will not be possible to identify you.

Making clinical trial data available to other investigators is encouraged – it allows maximum use to be made of any data generated and it can help with future research which may deliver benefits to patients. Other third party researchers may wish to access the anonymised data from this study in the future (anonymised data do not include names, addresses or dates of birth, and it is not possible to identify individual participants from anonymised data). For example, if future work is done by another group of researchers investigating treating fatigue in sarcoidosis patients

then they may wish to look in detail at the data we collected during this trial or analyse it in a different way, which may help with the design and conduct of their work. If external researchers wish to access the anonymised data, the Chief Investigator will ensure that the other researchers comply with legal, data protection and ethical guidelines.

Who will have access to my hospital (medical) notes?

Your hospital notes will only be seen by members of the trial team that work in the Norfolk and Norwich Hospital (this means that they are members of the respiratory medicine department and are either involved in looking after your care or work closely with the consultant who normally looks after your care, also referred to as the "direct care team"). Your notes will not be seen by anyone outside of the hospital.

If you join the study, the data collected for the study and any relevant medical records may be looked at by authorised persons from Norwich Medical School, the Research and Development Department of the Norfolk and Norwich Hospital and the Regulatory Authorities to check that the study is being carried out correctly. If your medical notes are reviewed by these bodies then the individuals doing so will have a duty of confidentiality to you as a research participant and confidentiality will be maintained throughout.

Informing your General Practitioner

With your permission, your GP will be informed of your participation in this study. We will also inform your respiratory consultant (the doctor looking after your sarcoidosis) if you have one.

Withdrawal from the study or early termination of the study.

The study doctor may have to stop your involvement in the study or remove your data from the analysis in certain circumstances for example should he/she find out that you shouldn't have been included in the study in the first place. In addition, the sponsor may decide to stop the whole study. We will explain the reasons to you if you are withdrawn or the whole study is stopped. You can decide to stop taking part in the study at any time without this affecting your medical care. If you do decide to stop taking part then we would be grateful if you could complete a short questionnaire as this will provide important information when designing future studies.

What will happen to any blood samples that I give?

All of the blood tests will be securely collected, stored and analysed. Your blood samples will be tested to see if it is safe for you to continue taking the trial medication and to help you answer any research questions. The blood tests taken for safety will be processed the day it is taken. If it is not safe for you to continue taking the study medication we will let you know as soon as the result is available to

us. These blood tests, which are taken for safety, will include your name, age and hospital number on the labelling so that the blood can be processed in the usual way and will be available to the healthcare professionals directly involved in your care.

What will happen to the results of the research study?

The study will be written up as a research paper and will be submitted for publication in a medical journal. It will be presented by members of the research team at medical conferences. The results are important to determine whether conducting a future clinical trial of methylphenidate for treating fatigue is possible and would inform how best to go about this.

Who is organising the research?

The research is being organised by researchers from University of East Anglia and the Norfolk and Norwich University Hospitals Foundation Trust. The research is being funded by a research grant from the National Institute for Health Research (NIHR) awarded to Dr Atkins as part of a doctoral research fellowship (DRF) programme. The NIHR-DRF grant reference is DRF-2015-08-190. None of the researchers are being paid for recruiting patients into the study.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given favourable opinion by one of these committees (East of England – Cambridge Central, reference number 16/EE/0087).

In addition, the study has also been reviewed and approved by the Medicine and Healthcare Products Regulatory Agency (MHRA). The Research and Development department of your local hospital has also reviewed and approved the study.

What happens next?

If you are willing to participate then you will be asked to sign a consent form to confirm this. If you do not wish to participate at this point then we would like to thank you for reading this information and for having considering taking part this project.

Contact for further information

Researcher Contact Details:
Dr Chris Atkins, NIHR Doctoral Research Fellow, Norwich Medical School, University of East Anglia, Norwich, NR4 7UQ.
Email: c.atkins@uea.ac.uk

Chief Investigator Details:
Professor Andrew Wilson, Professor of Respiratory Medicine, Norwich Medical School, University of East Anglia, Norwich, NR4 7UQ.
Email: a.m.wilson@uea.ac.uk

To contact either member of the research team about this study please call us on 01603 289876 or 01603 286366 (Norfolk and Norwich University Hospital Respiratory Research Group), mentioning the study title. If we are not in the office when you call we will get back to you as soon as we can to discuss any queries you may have.

Helpline contacts

To report a trial side-effect or any untoward event related to the trial, phone: 01603 289876 (Monday to Friday, 9am to 5pm). For out of hours advice call Dr Chris Atkins or Professor Andrew Wilson via the hospital switchboard (01603 286286).

If you have more general questions about participating in research then please speak to your doctor, or contact the Public and Patient Involvement in Research (PPIRes) - phone 01603 257292 or visit http://www.nnuh.nhs.uk/Dept.asp?ID=265.

Thank you for taking the time to read this information leaflet

Norfolk and Norwich University Hospitals NHS
NHS Foundation Trust

Prof A M Wilson

Department of Respiratory Medicine

Norfolk & Norwich University Hospital

Colney Lane

Norwich

NR47UY

Website: nnuh.nhs.uk

Direct Dial: 01603 298639

Direct Fax: 01603 289640

Information about Respiratory Research – Participant Information Sheet

The Respiratory Research Team would like to invite you to take part in our research study. You do not have to take part if you do not want to. Before you decide we would like you to understand why the research is being done and what it would involve for you. Please read this information which will help you decide.

Title – A comparison of health status scores in patients with sarcoidosis

Short title – Measuring health status in sarcoidosis

What is the purpose of the study?
Sarcoidosis is a condition of unclear cause which can lead to symptoms that affect any part of the body, including the lungs, skin and joints. It can also cause problems such as excessive tiredness, muscle aches and pains, or weakness. Not everyone with sarcoidosis develops the same problems. It can affect different people in very different ways. Any of these problems can affect your quality of life – by quality of life, we mean a measure of how well (or unwell) your health makes you feel.

This study aims to compare some commonly used questionnaires which measure how problems with our health affect how well we feel. We would like to see if two of the most commonly used questionnaires (one called the *Short Form* 36 or SF36, and one called the *EuroQoL-5D*) are comparable in patients with sarcoidosis.

We would also like to compare the results from these questionnaires with three other questionnaires – one looks at the presence of certain symptoms that may be seen in sarcoidosis (the *Kings' Sarcoidosis Questionnaire*), one looks at the presence of fatigue and the severity of it (the *Fatigue Assessment Scale*), and a final questionnaire looks at symptoms of low mood or anxiety (the *Hospital Anxiety and Depression Score*). We hope to see whether the results of these three

questionnaires can predict how you view your quality of life – in other words, whether fatigue, low mood or other problems related to sarcoidosis can affect how you feel, and if so, by how much?

We hope that the results from this study will allow us to know more about how these questionnaires compare with each other, and which ones we should use in the future.

Why have I been invited?
You have been diagnosed with a condition called sarcoidosis.

Do I have to take part?
No. It is entirely up to you to decide. If you do not want to take part that's OK. Your decision will not affect the quality of care you receive.

What will I need to do if I take part?
If you agree to take part then we will ask that you do the following:

(1) Fill in some details regarding how long you have had sarcoidosis, how your sarcoidosis affects you, what treatment you are receiving for it, and whether you have ever smoked
(2) Complete five questionnaires which are contained within the questionnaire pack. You may complete these at home, or in the clinic if you have received the questionnaires whilst attending your hospital visit. Completing the questionnaires will take up to twenty minutes
(3) Return the sheet containing details about your sarcoidosis and the five questionnaires to us. This can be done using the enclosed pre-paid envelope if you have decided to complete the answers at home or alternatively return them to the front desk at the respiratory clinic (if you are in the hospital).

The questionnaires will be returned to the study team. Following this, you do not need to do anything else.

I have already received one set of these questionnaires, do I need to fill in another set?
If you have already completed a set of these questionnaires, either in clinic or having received them by post, you do not need to complete them again. ***You should only complete <u>one</u> set of questionnaires.***

What are the possible disadvantages and risks of taking part?
There are no risks associated with undertaking the questionnaires. If, having answered the questionnaires, you are worried about anything that you have said (or are worried about your health having answered the questions), please contact us using the telephone number or e-mail address at the end of this information sheet. Alternatively, any concerns about your sarcoidosis can be discussed with your consultant in clinic.

What are the potential benefits of taking part?
Whilst it is unlikely that there will be any direct benefit to you as an individual, the results will help advance medical knowledge in this area. At present we do not know how the questionnaires we are looking at compare with each other. Your participation may help us to choose the best questionnaires in future research studies when investigating patients with sarcoidosis, as well as identifying which problems and symptoms most commonly affect patients with sarcoidosis.

What happens when the research study stops?
After you have completed the questionnaires you will not be asked to do anything further. The results from this study may be used to inform future research, or be used as part of future studies. If you would like to get a copy of the results of the study, please contact the research team using the details below and we will send you a summary of the study findings once it is completed.

What data will be collected and stored and who will have access to personal identifiable data?
The data you enter into the questionnaires will be collected on a database which will be stored on secure computers in the Norfolk and Norwich University Hospital. No personal data, or data that could be used to identify you, is required in the questionnaires – you do not need to put your name or any other identifiable details (such as your date of birth or address) anywhere on the questionnaires. This means that all the data collected is anonymous; no personal data is returned on the questionnaires you complete and no personal data about you is stored.

Who is organising the research?
The research is being organised by the Respiratory Research team consisting of researchers from Norwich Medical School, University of East Anglia and Norfolk and Norwich University Hospitals Foundation Trust. None of the researchers will receive any payment or funding for including you in the study. The study forms part of a PhD for Dr Atkins which has been funded by a doctoral research fellowship from the National Institute of Health Research (grant number DRF-190-08-2015)

Thank you for your consideration of taking part in this study. If you are still interested, or have any further questions, then please contact the study team using the details at the bottom of this page.

You may also obtain more detailed information about this research by contacting us using the details below:
Dr Chris Atkins
Phone 01603 289876
c.atkins@uea.ac.uk
Respiratory Research Department, Hethel Ward Corridor, Level 3 East Block, Norfolk and Norwich University Hospital, Colney Lane, Norwich, NR4 7UY

Appendix 4 – Topic guide (focus groups – FaST-MP study)

<table>
<tr><td colspan="2">Focus group objectives

• To establish patient experience of participation in FaST-MP trial
• To identify shortcomings in the initial trial and generate ideas that might influence future trial design (key issues; anything that would influence participant enrolling in the trial)</td></tr>
<tr><td>Start</td><td>Introduction and housekeeping

• Welcome and thanks for coming
• Introduce moderator
• Scheduled for a 60 to 90 minute meeting; confirm everyone is OK with this
• Plan to break for refreshments half way through
• Identify the locations of facilities (toilets)
• Encourage people to help themselves to coffee, tea, water etc as needed</td></tr>
<tr><td></td><td>Presenting the purpose of the meeting

We are here today to talk about your views on your participation in the recent “Fatigue and Sarcoidosis – Treatment with Methylphenidate” trial. The purpose is to get your thoughts and feelings on how participation in the trial was for you – whether you felt participation was a positive or negative experience, whether there were any problems that you encountered being in the trial, what you didn’t like about it and how you think we might be able to improve a future trial.</td></tr>
<tr><td></td><td>Explain ground rules and roles

I was the study co-ordinator and designed the study. However, my role today is to guide the discussion and help sharing of your views – I am not here to give you my opinions.</td></tr>
<tr><td></td><td>Rules of Engagement</td></tr>
</table>

	• The focus group is a relaxed discussion, not a Question and Answer session • There are no right or wrong answers, and you can change your mind or opinions • The aim is to explore your experiences during the trial and possibly generate some ideas that might influence the design of future trials in this area • We are also interested in whether you felt that your fatigue was better whilst you were in the trial. • Please respect each other's contributions – no interruptions or side conversations • You should feel free to respond to each other's comments – you don't need to wait for me to invite you • The discussion is confidential – comments will not be attributed to everyone, so feel free to say what you really think • Please do not refer to each other by name to maintain confidentiality. You are all wearing badges with initials on – please use these when referring to each other • There will be no further commitment from you after the session
	Taping the Session • We would like to record the session today, to make it easier to capture everything faithfully which will allow us to make an accurate analysis afterwards • The notes will help us to establish how effective the treatment was for participants within the trial, how you found the trial and whether there are any changes we should make for any future trials
	Warm up • Participant introduction – where you have travelled from today, how long since you finished the trial
	Discussion topic 1 – Experience of the trial • What was the best thing about taking part in the trial? • What was the worst thing about taking part in the trial? • Was there anything in the trial design that put you off taking part at the beginning?

	• Was there any aspect of the trial that was particularly problematic for you? *Possible prompts if people initially don't voice any problems about taking part in the trial:* o *Number of visits to the hospital* o *Number of tablets to take* o *Difficulty with the size of the tablets* o *Difficulty performing the breathing tests or the walking tests* o *The number of questionnaires needing to be filled in* o *Filling in questionnaires that didn't seem to be relevant* • Did you have any problems wearing the activity monitors for the 7 day periods during the trial? • Thinking back on the experience of the trial, would you describe your experience as a positive one or a negative one? • If you had the option to continue the medication, would you want to? • Given the chance again, would you still take part in the trial?
	BREAK
	Discussion Topic 2 – Changes to the trial • Based on what was discussed in the previous in the previous topic, is there anything you would change about the trial if you could? *Possible prompts if people initially don't voice any suggestions of future changes to the trial:* o *Reduced number of visits to the hospital* o *Possibility of a reduced afternoon dose of medication* o *Not wearing the accelerometers for a week at a time* o *Reducing the number of questionnaires needing to be filled in* o *Removing questionnaires that didn't seem to be relevant – if so, which ones?* • Was there enough contact with the study team through the study?

	• Is there anything that would have made you happier to participate in the trial? *Possible prompts:* ○ *More contact with the study team* ○ *More safety visits* ○ *Shorter duration of the trial* ○ *The possibility of receiving the medication after the trial if benefit was shown during the trial* ○ *The possibility of receiving the active drug (methylphenidate) if randomised to the placebo arm initially (i.e. open label period where all participants are on the active drug)*
Finish	**Closure** • We've discussed a lot today and there have been a lot of opinions expressed. Some of the key points seem to include *(summarise some of the points made)*. • Does anybody see the discussion differently, or want to add or clarify anything? • Is there any information regarding your experience of the trial that we haven't discussed that you think would be useful to share? • Thanks for coming

Appendix 5 – Non-validated questionnaires

A comparison of two wrist-worn accelerometer devices for the measurement of activity in sarcoidosis patients

Date: **Patient ID:**

For the **[device name here]** [visual description of the device], please mark a cross on the line for each question.

1. **How comfortable was the device to wear?**

Very Comfortable		Very Uncomfortable

2. **How aware of it were you?**

Unaware		Very Aware

3. **Would you have any objection to wearing it again?**

No Objection		Never Again

4. **To what extent did it interfere with daily life?**

No interference		Interfered constantly

5. **If you encountered any difficulties, please comment below. If none were encountered, please leave blank. Thank-you.**

6. **Did you have to remove the device at any time? If so, for what reason? If you didn't remove the device, please leave blank**

A comparison of two wrist-worn accelerometer devices for the measurement of activity in sarcoidosis patients

Date: **Patient ID:**

Which device would you prefer to use if you had the choice of the two?

GENEActiv
(Black plastic device with blue back) ☐

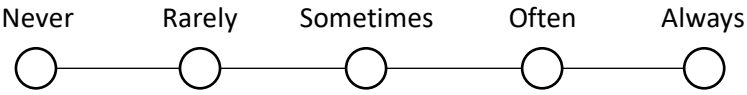
Actigraph
(Red device with Velcro strap) ☐

Safety Questionnaires

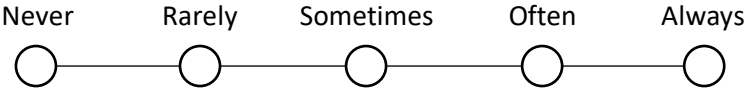
Please put a cross in the circle that best describes the following:

In the last fortnight, how frequently have you had any of the following problems?

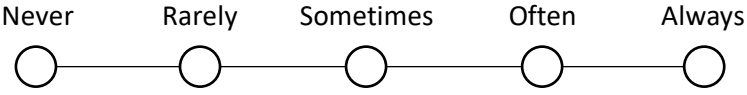
I have difficulty getting to sleep



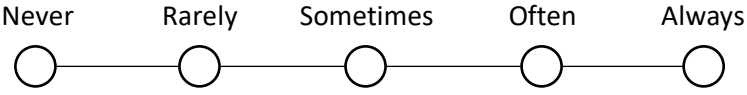
I have difficulty staying asleep



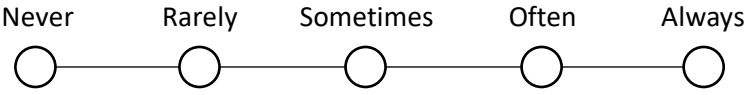
I feel jittery



I get palpitations



I get chest pains



Have you noticed any other problems since your last visit or since starting the study drug?

_____

_____

_____

_____

_____

_____

FaST-MP study - Exit Questionnaire

If you were given the choice to continue receiving the medication, would you want to?

Yes ☐ **No** ☐

Did you find participating in the study useful?

Yes ☐ **No** ☐

Given the chance again, would you still have taken part in this study?

Yes ☐ **No** ☐

Would you recommend taking part in any future study investigating methylphenidate for sarcoidosis-associated fatigue to other patients?

Yes ☐ **No** ☐