Study Protocol

Observational study of early diffuse cutaneous systemic sclerosis

(ESOS)

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LIST OF ABBREVIATIONS

ODP	Orphan Disease Programme
dcSSc	Diffuse cutaneous systemic sclerosis
mRSS	Modified Rodnan skin score
MMF	Mycophenolate mofetil
IV	Intravenous
ESR	Erthrocyte sedimentation rate
eGFR	Estimated glomerular filtration rate
CRP	C-reactive protein
FVC	Forced vital capacity
TLCO	Transfer factor of the lung capacity for carbon monoxide
PAP	Pulmonary arterial pressure
SHAQ	Scleroderma Health Assessment Questionnaire
FACIT-F	Functional Assessment of Chronic Illness Therapy - Fatigue
SF-36	Short Form 36 Health Survey
CHFS	Cochin Hand Function Scale

SUMMARY

Our objective is to examine the effectiveness of currently used approaches in the early management of patients with diffuse cutaneous systemic sclerosis (dcSSc) in a prospective observational study, capturing entry and outcome data in a standardised way. An observational approach has been used successfully in studies of several diseases and, in the UK, we have piloted this observational approach in a study of 147 patients with dcSSc and confirmed its feasibility. However, much larger numbers of patients are required to answer key questions about the effectiveness of different immunosuppressant treatments. With an estimated 2,500 new cases/year of dcSSc across Europe, this will be possible within a multicentre European study.

Patients will be eligible for inclusion into the study if skin thickening (scleroderma) is of less than 3 years duration, which is when the disease is most likely to progress rapidly. Treatment, in all cases, will be decided by clinicians and patients as per usual clinical practice. The active treatments to be observed within this study, as decided by an international steering committee, are mycophenolate mofetil (MMF), cyclophosphamide and methotrexate. Patients who do not receive an immunosuppressant therapy will also be observed.

Following informed consent, each patient is followed up at set time points for 12-24 months, with regular checks, including careful documentation of any changes in therapy. This is a 'real life' approach; a patient may change therapy within the study if, for example, s/he develops side effects to the first treatment tried. The primary outcome variable will be the modified Rodnan skin score (mRSS) and secondary outcome variables will include routine laboratory parameters, assessments of lung, cardiac and renal function, and a set of validated quality of life measures. The assessments and tests from which data will be collected are embedded within routine clinical practice and no additional procedures will be involved as part of this study. Treatment outcomes 12 months and (when available) 24 months after the study start will be compared using modern statistical techniques including marginal structural models. Inverse probability of treatment weights will allow for differing patient characteristics between groups.

1. INTRODUCTION

1.1 Background

Early dcSSc is associated with high morbidity and mortality. Patients with this subtype of systemic sclerosis (SSc) [1] experience rapid progression of skin thickening, commencing distally but going on to involve proximal limb and/or trunk. The 5 and 10 year survival rates for patients with dcSSc are in the order of 74% and 66% respectively, as estimated from the Pittsburgh database [2]. Given that the peak age of onset is most commonly in the fifth decade, life expectancy is often significantly reduced. The burden of disease in terms of morbidity is substantial: patients with early dcSSc are at risk of pulmonary, cardiac and renal involvement [3], all of which can have a major impact on quality of life. The widespread skin thickening of early dcSSc can also be extremely painful and disabling, restricting mobility and hand function and leading to ulceration over pressure points, for example over the proximal interphalangeal and metacarpophalangeal joints.

Although the prognosis in individual patients as regards long-term survival can be good, 10 year survival is only 66%. More importantly the proportion with end-organ damage free survival is much lower. There can be no doubt that improving severe disease-free survival in patients with dcSSc, by identifying effective treatments, is an important and key goal for clinicians and scientists with an interest in SSc.

At present, there is no drug known to favourably influence disease course. The EULAR Scleroderma Trial and Research Group (EUSTAR) recommendations advocate methotrexate for skin disease [4] yet this agent has been shown to be of only limited efficacy [5]. Stem cell transplantation is currently being evaluated [6,7] but, even if effective, is likely to be restricted to a minority of severe cases with evidence of significant internal organ involvement. Anecdotally, most clinicians favour immunosuppression. There is a sound scientific rationale for this, because early dcSSc is associated with immune dysfunction and inflammatory change [8] however there is no good evidence base for this approach. Thus a key aspiration for those treating dcSSc is an enhancement of the evidence base to inform rational therapeutics.

1.2 Rationale for study

An important factor underlying the failure to identify an effective disease-modifying agent for early dcSSc is the difficulty involved in mounting controlled clinical trials. The rarity of early dcSSc means that trials must be multicentre in order to achieve adequate levels of recruitment and pharmaceutical companies are often reluctant to invest in trials of rare or ‘orphan’ disease. Clinicians and patients alike are frequently reluctant to recruit into studies in which a patient might be randomised either to placebo or to a drug where there is an a priori reason of lesser effect than an alternative – even though there is at present no known effective disease-modifying therapy.

Furthermore, the typically strict inclusion and exclusion criteria of randomised controlled trials of immunosuppressive treatments often result in patients with significant internal organ involvement being excluded. Given the multisystem nature of dcSSc, this means that many of the patients in whom a disease-modifying drug is most needed are excluded. Evidence for the difficulty of recruiting into randomised controlled clinical trials of early diffuse disease comes from the small numbers of patients recruited into well-designed, multicentre trials conducted in the last 10 years: the alpha-interferon study recruited 35 patients (multicentre, UK only) [9]; the high-dose versus low-dose penicillamine study 134 patients (17 centres, US only) [10]; the methotrexate study 71 patients (multinational) [5]; the transforming growth factor (TNF)-beta study 45 patients (multinational) [11]. The ASTIS (Autologous Stem Cell Transplantation International Scleroderma Trial), which has been recruiting since 2001, has recruited 150 patients. Assuming an incidence rate of SSc in the order of 20/million, with approximately a quarter of new cases being of dcSSc, then the number of new dcSSc cases in the European Union alone could be as high as 2,500 per year [12,13]. Given the small numbers of patients recruited into controlled trials, this does raise questions about what is happening to these other patients with dcSSc who are not recruited into controlled trials. The most likely scenario is that, in different countries, patients with early dcSSc are being treated with a variety of different immunosuppressants, according to physician preference and yet without a good

evidence base. For a life-threatening disease, this is highly unsatisfactory and we need to capture information on treatment outcome in at least a proportion of these patients.

Our objective is to examine the effectiveness of currently used approaches in the management of patients with early dcSSc in a prospective, observational study. Such an approach has recently been advocated by the Head of the UK's drug approval body NICE (National Institute for Clinical Excellence: an organisation committed to basing drug approvals on the highest standards of evidence) as an appropriate substitute for randomised trials in rare disorders such as SSc for which there is a serious lack of data from randomised clinical trials [14]. The underlying concept is that treatment choice is one of the variables influencing disease outcome, which can be dissected by collection and analysis of data that are routinely collected in services offering high quality care. Treatment, in all cases, will be decided by clinicians and patients in accordance with routine clinical practice. The active treatment protocols to be observed (following informed consent) within this study, as decided by an international steering committee, are MMF, cyclophosphamide and methotrexate. Patients who do not receive an immunosuppressant therapy will also be observed in a 4th protocol. Patients will then be followed up at regular time points for a period of 12 -24 months, again in accordance with best clinical practice for patients with dcSSc. This observational approach does not compete with randomised controlled trials but is, instead, complementary to these [15] and is designed to run in parallel. Judging from recent experience (cited above), it is unlikely that more than 50 patients per year across Europe would be recruited into randomised controlled trials of immunosuppressive treatments for early dcSSc. This would leave the majority of patients 'available' for recruitment into an observational study.

In the UK, we have already piloted this observational approach within a multicentre UK study and so can affirm its feasibility and the statistical robustness of the approach for adjusting for patient baseline and follow-up difference in treatment allocations [16]. The conclusion of this study was that all treatment protocols studied, including that initially offering no immunosuppressant therapy, were associated with similar falls in skin score – the main pre-specified outcome measure. However, the numbers were too modest for robust evaluation.

The goal of this multicentre study is to recruit large cohorts of patients from several European centres into an observational study including most commonly used immunosuppressive regimes and to compare their effectiveness. Recruitment from multiple centres and countries will ensure a wide variation in therapeutic choices and will allow for the situation that, within a particular centre, all patients are treated according to the same treatment protocol. The advantage of the observational approach is that it is designed to 'bolt on' to local clinical practice to minimise the issues of ethics and governance that can deter participation in standard trials and to 'capture' patient experience that is currently lost. A large European collaborative observational study is, therefore, a pragmatic, affordable and scientifically appropriate choice for answering key questions about the relative effectiveness of immunosuppressive therapy currently used. The study will also raise awareness of the importance of early diagnosis, referral, and assessment of patients with early dcSSc because participating clinicians across different countries will encourage colleagues to identify patients fulfilling the inclusion criteria.

2. STUDY OBJECTIVE

To compare the effectiveness of different immunosuppressant treatments currently favoured by clinicians treating early dcSSc through the careful recording and analysis of routinely collected clinical data.

3. ENDPOINTS

3.1 Primary Endpoint

Change in mRSS between a baseline assessment at 0 months and at 12 months is the primary endpoint. Data will also be available at 24 months for a proportion of the patients recruited.

3.2 Secondary Endpoints

These are all part of routine clinical practice:

Haemoglobin, ESR, plasma creatinine, eGFR, CRP and urinary dipstix at 3 monthly intervals.

Pulmonary function tests at baseline, 12 and 24 months.

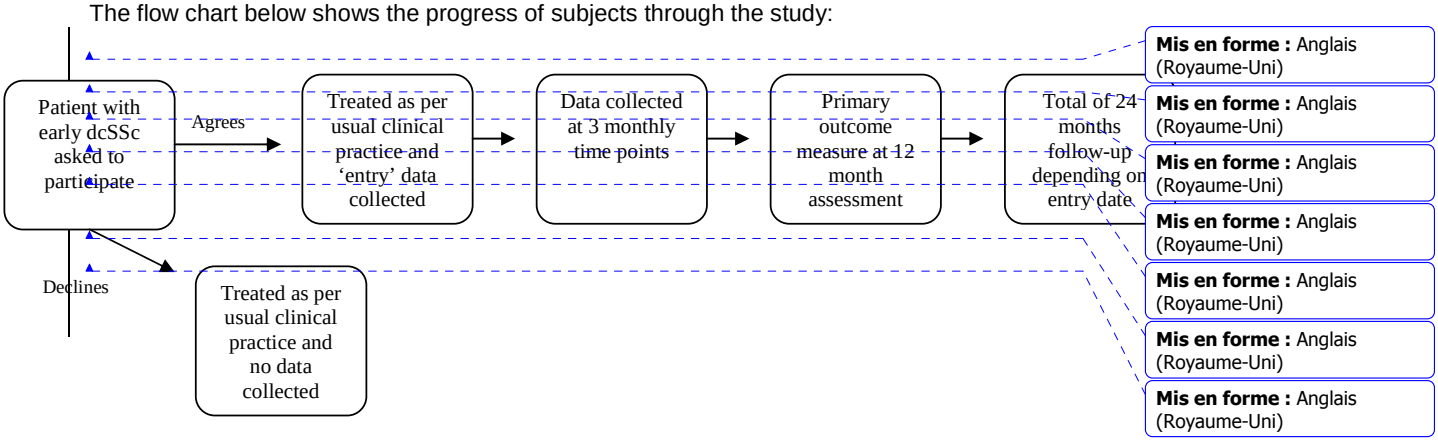
Echocardiogram at baseline, 12 and 24 months, with estimated PAP on echo.

Quality of life functional assessments at baseline, 12 and 24 months consisting of the Scleroderma Specific Health Assessment Questionnaire, the FACIT-F, the Short Form 36 Health Survey and the Cochin Hand Function Scale.

4. STUDY DESIGN

This is an observational prospective study. Treatment, in all cases, will be decided according to usual clinical practice. Clinicians at participating centres across Europe will approach patients with early dcSSc who meet the study criteria and whose treatment will meet one of the four treatment protocols observed within the study. The protocols reflect current treatment strategies and were chosen by an international steering committee. Following informed written consent, patients are then followed at regular intervals for a total of 12-24 months, in keeping with best clinical practice, and data entered via a secure web-based system. The data from patients across Europe are then collated and analysed by statisticians at the University of Manchester.

The flow chart below shows the progress of subjects through the study:



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5. STUDY POPULATION

5.1 Number of participants

The recruitment period is 24 months from July 2010 to June 2012 (inclusive), with an emphasis on the first year (to June 2011) during which it is hoped that most patients will be recruited.

The target number of participants for each treatment protocol is 100 with an overall total of 400 participants. The absolute minimum number of patients needed is 316.

Eight primary recruitment sites are located across Europe, with additional sites to be included between February and July 2010.

5.2 Inclusion criteria

- Diffuse cutaneous SSc.
- Age > 18 years.
- Skin involvement of less than 3 years defined by patient report or clinician opinion.
- Patient and clinician able and willing to conform with the requirements of at least one of the treatment protocols.

5.3 Exclusion criteria

- Previous use of stem cell transplantation.
- Previous use of more than 4 months of methotrexate, MMF, cyclophosphamide or other immunosuppressant treatment.
- Previous use of immunosuppressant therapy other than methotrexate, MMF or cyclophosphamide within previous month.

6. PATIENT SELECTION AND ENROLMENT

6.1 Identifying patients

Potential participants will be identified by the different clinical teams across sites through review of clinical notes and referral letters.

6.2 Consenting patients

Informed written consent will be taken by clinicians or research nurses within different sites following an explanation of the patient information sheet. A copy of the consent form will be retained as part of the study data.

6.3 Screening for eligibility

Patients who fulfil the study inclusion criteria and who sign informed consent forms will be followed for the duration of the study.

6.4 Ineligible and non-recruited patients

Patients who do not fulfil the criteria, or who do not wish to take part in the study, will receive the same clinical care to the same standard as patients who do take part in the study.

7. TREATMENT

7.1 Treatment protocols to be observed

The study will observe four treatment protocols commonly used within clinical practice. Three consist of active immunosuppressant treatment;

1. MMF. Recommended dose 500mg twice daily for 2 weeks increasing to 1gm twice daily.
2. Cyclophosphamide. Possible regimes within this protocol include:

(i) IV. Minimum monthly dose 500mg/m^2 with a recommended duration of 6-12 months.

(ii) Oral. 1-2mg/day with a recommended duration of 12 months.

3. Methotrexate. Either oral or subcutaneous with a target dose of 20-25mg weekly.

The 4^{th} protocol to be observed within the study is 'no immunosuppressant treatment'.

7.2 The use of other medications

The use of additional treatments will be documented by clinicians at each visit.

Patients may take the following medications during the 12-24 month observation period (concurrently with any of the four treatment protocols):

Prednisolone (the dosage should not normally exceed 10mg/day).

IV prostanoids.

Biological therapy for inflammatory arthritis.

Hydroxycholoroquine.

Non-immunosuppressant treatments

If a patient commences an immunosuppressant treatment other than MMF, cyclophosphamide or methotrexate (including stem cell transplantation) or a biological therapy (other than for an inflammatory arthritis overlap) then s/he is withdrawn from the study as below.

7.3 Changes between protocols

If clinicians and patients decide to move from one protocol to another, all primary outcome measures will be documented at the time of protocol 'switch', with a one month period between the two protocols. This is, again, in keeping with good clinical practice. It is anticipated that changes in protocol may take place between study visits. Where this involves an additional clinic visit, clinicians will be asked to document all outcome measures and enter them into the web-based system. Where changes in protocol take place without an additional visit, clinicians will be asked to document outcome measures as far as possible.

Patients may also (as per usual practice) take part in studies involving the use of different therapies and, as long as this does not involve an additional immunosuppressant treatment, this data will be collected and the patient will continue to be observed as usual within this study.

Reasons for terminating any one of the 4 treatment protocols will be documented in 3 main groups:

1. Development or progression of major organ-based complication
2. Clear progression of skin disease
3. Adverse event

7.4 Withdrawal from the study

If a patient commences a form of immunosuppressive treatment not included in the four protocols, stem cell transplantation or biological therapy (other than for concomitant inflammatory arthritis), all outcome measures will be documented and recorded and the patient will be 'withdrawn' from their treatment protocol. Data will continue to be collected at the usual set time points for the 12-24 month observation period.

If a patient wishes to withdraw completely from the study, no further information will be collected about their treatment.

7.5 Adverse events related to medication

Data will be collected by different clinicians on adverse events and side effects relating to the use of the different treatment protocols as per routine clinical practice. As this is an observational study, and does not therefore involve the use of experimental medications or treatments that the patient would not receive as part of their routine care, there is no onus to report adverse event data in the manner of a randomised clinical trial but data will be collected as appropriate and will form an integral part of the final analysis.

8. STUDY ASSESSMENTS

Patients will be assessed at 3 monthly intervals for a maximum of 24 months. At each time point (shown in the table below) data from best routine clinical practice will be recorded. Patients will also be asked to complete a series of pen-and-paper measures documenting quality of life and physical function while attending routine clinical appointments at baseline, 12 and 24 months.

	Visit 1 0 month (Baseline)	Visit 2 3 month	Visit 3 6 month	Visit 4 9 month	Visit 5 12 month	Visit 6 15 month	Visit 7 18 month	Visit 8 21 month	Visit 9 24 month
mRSS	**X**	**x**	**x**	**X**	**x**	**x**	**x**	**x**	**x**
Internal organ involvement	**X**	**x**	**x**	**X**	**x**	**x**	**x**	**x**	**x**
Haemoglobin, ESR,	**X**	**x**	**x**	**X**	**x**	**x**	**x**	**x**	**x**

plasma creatinine, eGFR, CRP, urinary dipstix									
FVC, TLCO	X				x				x
Estimated PAP	X				x				x
SHAQ	X				x				x
FACIT-F	X				X				X
SF-36	X				x				x
CHFS	X				x				x

9. DATA COLLECTION

Clinical and demographic data will be collected by members of the direct clinical team from clinical notes or databases. All data collected forms part of best routine clinical practice. Clinical data will be entered onto an electronic case report form within a secure web-based data collection system managed and maintained by the University of Manchester. The web system will contain a 'print screen' function that will allow clinicians to print hard-copy paper case report forms for completion within outpatient clinics and also for their own records but all clinical data entry will be electronic. The electronic case report forms are, therefore, considered to be the source data, with the exception of patient questionnaires which will always be completed in hard-copy paper form and entered into the web-based system at a later date. The patient questionnaires are the source documents in this instance and must be retained by participating centres for monitoring purposes.

Data entered onto the web-based system is securely transferred to the University of Manchester. There will be inbuilt data quality mechanisms within the web-based system e.g. to 'force' correct data entry in terms of limiting missing or inconsistent values. This will allow the study coordinator to identify and correct errors and inaccuracies quickly, and monitor data quality throughout the study. The system is also designed to avoid the transfer of clinical data via unsecure methods such as fax or email.

10. STATISTICS AND DATA ANALYSIS

10.1 Sample size calculation

The aim will be to identify as significant a difference between any two therapeutic paths of at least 5 Rodnan skin score points. This will require 63 patients to be recruited into each protocol and followed for the requisite period of time. Allowing for an estimated drop out rate of 20% the aim will be to recruit 79 patients per arm.

10.2 Proposed analyses

In an observational study design, treatment groups may differ at baseline and differences in outcome may be partly due to differences in treatment, and partly due to the fact that different treatments tend to be given to different types of people. Statistical analysis has to separate out the 'between-treatment' differences and the 'between-person' differences.

Adjusting for differences at baseline is relatively straightforward. One option is to include all potential confounders (variables that affect both outcome and treatment allocation) in a regression model. However, this depends on knowing how the confounders affect the outcome: if the regression model is incorrectly specified, there will still be residual confounding. An alternative approach involves reweighting the data to make the distribution of all potential confounders the same in all of the treatment groups [17]. Provided that there are no confounders that are not measured, a simple comparison of treatment effects in the weighted data will be unbiased. Weights can be calculated based on the probability of receiving a particular treatment given a subject's covariates, which is known as the propensity score [18]. This is the most flexible method of adjusting for differences between protocol groups.

Furthermore, in an observational study, subjects may change treatment during the course of the study, and these changes in treatment may be influenced by changes in the potential

confounders (or by changes in the outcome variable, in this case the skin score). The differences in outcome between treatment groups may be due in part to selection by these changing confounders, so if these are not taken into account, it may result in a biased estimate of the differences between treatment groups. However, these cannot simply be included in a regression model, since they will have been affected by prior treatment, so adjusting for them will adjust away some of the treatment effect.

Weighting will allow for changes in the confounders leading to changes in treatment by weighting. Each time that a subject changes treatment, all potential confounders are measured, and their probability of receiving each possible treatment, based on their covariates at that time, is calculated. This treatment is referred to as marginal structural modelling [19]. A weight can be calculated for each subject based on the probability of their treatment history given their covariate history, and a comparison of treatments in this weighted data will not be confounded by any of the variables used in calculating the weights.

For the purposes of the statistical analysis, all variables thought to affect treatment outcome must be measured, and used in calculating the weights. It is not necessary to know exactly how baseline variables affect outcome for the purposes of the propensity methods. It is also important that patients within each treatment protocol are as similar as possible for the purposes of the analysis. The primary analysis will look at absolute differences in MRSS between treatments, but the relative change will also be considered, since there are likely to be differences in initial MRSS between treatments.

The data will be monitored throughout the study and an interim analysis will also be carried out by an oversight board to assess the data collected, and to check that the study aims can be met.

11. STUDY MANAGEMENT AND OVERSIGHT ARRANGEMENTS

11.1 Steering committee

The study will be coordinated by a steering committee, consisting of the grant holders (Dr Ariane Herrick, Professor Chris Denton, Professor Luc Mouthon, Professor Alan Silman, Dr Roger Hesselstrand and Dr Mark Lunt), two patient representatives (Ms Kim Fligelstone and Mrs Edith Brown), 2 allied health professionals (Mr Will Gregory and Ms Rachel Ochiel) and 4 other consultant clinicians (Dr László Czirják, Dr Oliver Distler, Dr Jörg Distler and Dr Madelon Vonk). Contact details are detailed in Appendix 1.

11.2 Study coordination

A study coordinator (Dr Holly Ennis) will oversee the study and will be accountable to the chief investigator (Dr Ariane Herrick) and the study steering committee. The study coordinator will be responsible for checking completed electronic case report forms for completeness, plausibility and consistency. Any queries will be resolved by investigators in conjunction with the study coordinator. The arc Epidemiology Unit at the University of Manchester will be responsible, through the study coordinator, for the collection of data, data processing and analysis. Publication and dissemination of the study results with be coordinated by the chief investigator, the steering committee and the investigators.

11.3 Oversight board

An independent oversight board will be established to oversee the quality of data collected during the study and assess the feasibility of the study objectives. The terms of reference of the oversight board and the names and contact details are detailed in Appendix 2.

11.4 Inspection of records

Study data and material may be looked at by individuals from the University of Manchester and from the relevant regulatory authorities for monitoring and auditing purposes, and this may well include access to personal information, such as consent forms.

11.5 Study monitoring

The study coordinator may make monitoring visits prompted by inconsistencies or unexpected values reported in electronic case report forms and, particularly, in the mRSS (the primary outcome measure).

A copy of the monitoring plan is given in Appendix 3.

11.6 Risk assessment

This is an observational study and clinicians will treat patients as per normal clinical practice. The main ethical issue is the transfer of clinical data from centres to the coordinator via a web-based system. A secure website and data collection system will be established to ensure that data is transferred safely and securely. Each patient entered into the study will be assigned a unique identification number. When contacting centres and clinicians, the study coordinator will not use identifiable information in correspondence either by letter or email unless it is encrypted.

12. STUDY CONDUCT

12.1 Ethical conduct of the study

The study will be conducted in accordance with the principles of the International Conference on Harmonisation/WHO Good Clinical Practice (ICH-GCP) guidelines.

A favourable ethical opinion from the relevant regulatory authorities will be obtained prior to commencement of the study and the collection of data. Each participating centre will be responsible for ensuring all local and regional research governance and legal requirements are met and to provide evidence before recruitment into the study can commence.

12.2 Investigator responsibilities

Investigators are responsible for the overall conduct of the study at each participating site and for compliance with the protocol and any protocol amendments. In accordance with the principles of ICH-GCP, the following areas listed in this section are also the responsibility of investigators.

12.2.1 Informed Consent

Investigators are responsible for ensuring informed consent is obtained before any patient can be enrolled in the study and data collected. The decision of a patient to participate in the study is voluntary and should be based on a clear understanding of what is involved.

Patients must receive adequate oral and written information – appropriate patient information and informed consent forms will be provided.

The patient must be given every opportunity to clarify any points s/he does not understand and, if necessary, ask for more information. The patient must be given sufficient time to consider the information provided. It should be emphasised that the patient may withdraw their consent to participate at any time without their clinical care being affected in any way. Investigators and patients should sign and date the informed consent form to confirm that consent has been obtained and a copy of this form should be kept as part of the study records. It is accepted that regulatory requirements may differ between participating centres.

12.2.2 Study Site Staff

Investigators must be familiar with the protocol and the study requirements. It is the investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the protocol and their study related duties.

12.2.3 Data Recording

Investigators are responsible for the quality of the data recorded in the electronic case report form. The quality of the mRSS, as the primary end point, is of particular importance and will be monitored closely. Additional support and training will be available as appropriate.

12.2.4 Investigator Documentation

Prior to beginning the study, each investigator will be asked to provide particular essential documents to the Sponsor, including but not limited to:

- Curriculum vitae (CV) signed and dated by the investigator indicating that it is accurate and current.

The chief investigator, with the agreement of the Sponsor, will ensure all other documents required for compliance with the principles of GCP are retained in a study master file and that appropriate documentation is available in local site files.

12.2.5 Confidentiality

All reports, and other records must be identified in a manner designed to maintain patient confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the patient, except as necessary for monitoring and auditing by the Sponsor and the relevant regulatory authorities. Investigators and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

12.2.6 Data Protection

In the UK, all investigators and study site staff involved with this study must comply with the requirements of the Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Access to collated participant data will be restricted to those clinicians treating the participants. Outside the UK, investigators and study site staff should comply with the relevant regulatory regulations regarding data protection.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data that could allow identification of individual participants.

12.2.7 Protocol amendments

Amendments to the protocol must be submitted in writing to the appropriate regulatory authorities.

12.2.8 Study record retention

The University of Manchester policy on storage of personal data is 5 years after the last publication of the study or for 10 years, whichever is the greater. Consent forms will be retained as essential documents, but items such as contact details will be deleted as soon as they are no longer needed.

12.2.9 End of study

The end of study is defined as the last participant's last visit.

The end of the study will be reported to relevant regulatory authorities.

12.2.10 Publication

It is anticipated that, where at all possible, all investigators will be co-authors in any resulting publication.

12.2.11 Peer review

The study has undergone a rigorous process of peer review within the University of Manchester's School of Translational Medicine and by EULAR, the body awarding the grant supporting this study.

13. REFERENCES

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APPENDIX 1: STUDY STEERING COMMITTEE

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APPENDIX 2: OVERSIGHT BOARD PLAN

The oversight board membership has yet to be confirmed but will consist of two clinicians with knowledge of SSc and a statistician with knowledge of the methods of analysis used within this study.

The oversight board will meet at least once annually (more often at the discretion of the board).

Decisions will be made by consensus.

Additional meetings or teleconferences of the board can be conducted at the request of the steering committee.

A designated member of the board will be responsible for preparing an agenda and minutes. The minutes should include i) date, time and location of the meeting; ii) attendees; iii) summary of the type of data reviewed and results; iv) summary/recommendations of the board. A copy of the minutes should be forwarded within 30 calendar days to the chief investigator/study coordinator who will keep a copy in the master study file and communicate the recommendations and decisions to the steering committee.

All documents containing results must be stored in a locked area, shredded or returned to the study coordinator at the end of the meeting. All documents should be marked 'confidential – do not copy'.

At the completion of the study, all original copies of the minutes, analyses and reports must be forwarded to the study coordinator for inclusion in the permanent study file.

If the board recommends a change in the protocol or in the conduct of the study the steering committee will convene (via teleconference or at a meeting) and discuss the reasons for the recommendation. If such action is not accepted by the steering committee, a written explanation will be sent to the board within a week. This decision will be made in conjunction with EULAR.

APPENDIX 3: MONITORING PLAN

The purpose of this monitoring plan is to provide assurances that the study is being conducted in accordance with the protocol, and that the data are as complete as they can be at the time of monitoring and that the data are accurate and verifiable.

Data quality control measures: All efforts will be made to ensure accurate data entry. Forms will be designed so that questions and response fields are unambiguous, clearly worded, and easy to read. There will also be detailed specifications for electronic case report form completion including rules for skipped questions and missing data, and detailed coding manuals with easy to remember codes. Training on the electronic data entry system for centres has yet to be finalised but will include a detailed manual with 'screengrabs' and the study coordinator will be available via telephone and email to assist where possible. Training visits and web-based training recordings are other possibilities.

Central monitoring: The study coordinator will monitor all data transferred via the web-based system to verify the entries by different centres. This monitoring will include computer edits to check out of range codes and tests of internal inconsistencies, comparisons of study identification numbers registered in the study and study identification numbers entered on electronic case report forms, and incremental data reviews to compare centres to determine variations between them in responses to questions on the electronic case report forms. Queries about inaccurate or inconsistent data will be identified by the study coordinator who will then email or telephone centres to clarify. If consistent variations are identified in data sent by centres, particularly in relation to skin scores, the study coordinator may arrange a monitoring visit or liaise via telephone or email to discuss the matter with centres and arrange additional support or advice as appropriate. In correspondence about particular cases, no subject names or personal identifiers will be used in emails or letters. Instead, participants will be identified using the unique study identification numbers, date of entry, age and initials.

APPENDIX 4: PARTICIPATING CENTRES AND LEAD CLINICIANS

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