Understanding and Treating Musculoskeletal Systemic Lupus Erythematosus

By

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The candidate confirms that the work submitted is his own and that appropriate credit has been given where reference has been made to the work of others.

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.

Abstract

Background: Musculoskeletal manifestations are common in Systemic lupus erythematosus. Most patients with inflammatory pain have no objective abnormality detectable by current clinical tools. Also, these tools may be poorly responsive. This is important because physicians need to decide when to start, increase or decrease immunosuppression for arthralgia. Imaging modalities such as ultrasound and magnetic resonance imaging have a promising role to solve these issues.

Objectives: (1)define and quantify inflammatory musculoskeletal phenotypes in SLE; (2) to evaluate the accuracy and responsiveness of existing outcome measures; (3)determine whether patients with ultrasound-only synovitis are more responsive to therapy; (4) determine whether ultrasound is a more responsive outcome measure than the other tools; (5) to validate Ultrasound against MRI.

Methods: (1) Consecutive SLE patients were evaluated clinically and by ultrasound synovitis; (2) a pilot longitudinal study was performed in 20 patients receiving glucocorticoids; (3) a definitive study (USEFUL) was performed in 133 patients to determine the responsiveness of ultrasound and other musculoskeletal variables, and predictive value of baseline ultrasound; (4) MRI scans were performed in 36 patients with varying degrees of clinical and US-synovitis.

Results: (1) most patients with active musculoskeletal symptoms did not have clinical synovitis on examination and a large group of patients with subclinical synovitis found only using ultrasound was associated with worse symptoms and serology; (2) clinical instruments underestimated ultrasound-confirmed response to therapy; (3) the USEFUL study showed that patients with baseline ultrasound synovitis had better responses to therapy as long as fibromyalgia was excluded. Ultrasound remained highly responsive, with varying degrees of responses in clinical instruments, but this did not correlate with patient-reported improvement; (4) MRI synovitis was confirmed in patients with ultrasound-only synovitis.

Conclusion: Ultrasound provides an accurate objective measure of synovitis in lupus patients and could be used to improve patient care and clinical trials

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Abbreviations

ACPA	Anti-Citrullinated Peptide Antibody
ACP	Acid Phosphatase
ACR	American College of Rheumatology
ADCC	Antibody-dependent cell-mediated cytotoxicity
ANA	Anti-nuclear antibody
APRIL	A PRoliferation-Inducing Ligand (tumor necrosis factor ligand superfamily member 13)
AZA	Azathioprine
BAFF	B-cell Activating Factor of the tumour necrosis factor of the ligand Family (tumor necrosis factor ligand superfamily member 13B)
BICLA	British Isles Assessment Group-based Combined Lupus Assessment
BILAG	British Isles Lupus Assessment Group
BlyS	B-lymphocyte stimulator
CCP	Cyclic citrullinated peptide
CD	cluster of differentiation
cDMARDs:	Conventional synthetic disease modifying anti-rheumatic drugs
CLASI:	Cutaneous Lupus Erythematosus Disease Area and Severity Index
CLE	Cutaneous Lupus Erythematosus
CNS	Central nervous system
CR	Conventional radiography
CRP	C-reactive protein

DAS-28	Disease Activity Score in 28 joints
DC	Dendritic cell
dsDNA	double stranded deoxyribonucleic acid
EBV	Epstein-Barr virus
EMS	Early morning stiffness
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FCGR	Fc fragment of IgG receptor
FM	fibromyalgia
GIT	Gastro intestinal tract
GS	Grey-scale
HC	Healthy control
HCQ	Hydroxychloroquine
HLA	human leukocyte antigen
IFN:	Interferon
IFNAR:	Type 1 interferon receptor
IFN-I	Type 1 interferon
IFN-II	Type 2 interferon
IFN-III	Type 3 interferon
IL	Interleukin

IQR	Interquartile range
ITGAM	Integrin alpha M
IV	Intravenous
mAb	Monoclonal antibody
MCP	Metacarpo-phalangeal joint
MHC	Major histocompability
MIR	MicroRNA
miRNA	Micro ribonucleic acid
MMF	Mycophenolate Mofetil
MSK	Musculoskeletal
MTP	Metatarso-phalangeal joint
MTX	Methotrexate
NICE	National Institute for healthcare and Clinical Excellence
NSAID	Non-Steroidal Anti Inflammatory Drugs
OMERACT	Outcome measures in rheumatoid arthritis clinical trials
OR	Odd ratio
PD	Power Doppler
Qol	Quality of life
RA	Rheumatoid arthritis
RCT	Randomised controlled trial

SLE	Systemic Lupus erythematosus
SELENA	Safety of Estrogens in Lupus National Assessment
SLAM	Systemic Lupus Activity Measure
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SRI	Systemic Lupus Erythematosus Responder Index
STK17A	Serine/threonine-protein kinase 17A
TGFB	Transforming growth factor beta
TNF	Tumor necrotizing factor
TLR	Toll-like receptor
UK:	United Kingdom
UV	Ultraviolet light
VAS	Visual analogue score

Chapter 1: Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune condition that causes significant morbidity and mortality [1]. Musculoskeletal manifestations are among the most common features of systemic lupus erythematosus (SLE) both in initial diagnosis and in long-term management. They are crucial to the overall patient outcome as well as the development of new therapeutics. Musculoskeletal manifestations of SLE are the first symptom in up to 50% of SLE patients and affect up to 95% during the clinical course. My thesis dissects musculoskeletal presentations in SLE looking at the best way to assess then aiming to incorporate imaging in assessment and validating outcome measures in SLE.

Accurate assessment of disease activity (e.g. synovitis) and joint damage (e.g. bone erosion) are imperative in rheumatology. Finding a tool that provides a sensitive and accurate measurement of inflammation and damage with the ability to discriminate between diseases and offer prediction and evaluation of outcome is a consistent demand in rheumatology to guide treatment decisions.

Recent clinical trials in SLE have cast doubt on the existing outcome measures. Rituximab was not proven to be effective in randomised controlled trials, but is widely believed to be effective. Belimumab(Anti CD20), epratuzumab(Anti CD22) and anifrolumab(Anti type I interferon) all demonstrated different outcomes in phase II and phase III trials, and data suggested outcome measures were partially responsible for this. Since approximately 90% of patients in non-renal trials had musculoskeletal disease activity this organ system is an important factor.

In SLE there is a lower frequency of clinical synovitis than in rheumatoid arthritis(RA), which is a challenge in the identification of patients amenable to immunosuppressive therapy, as well as in the assessment of response in clinical trials and routine practice [2]. In the various forms of the systemic lupus erythematosus disease activity index (SLEDAI) this is accounted for by the inclusion of tender, erythema or warmth to define synovitis, as well as just joint

swelling. In total, 4 points are scored for two or more joints with these signs (SLEDAI-2K) or more than two joints (SELENA–SLEDAI), and no points for lesser degrees of inflammation. However, these signs are more subjective than joint swelling and partial response cannot be captured. In clinical trials of belimumab an endpoint primarily based on the SLEDAI called the SLE responder index (SRI) was developed and has been used in trials of other agents [3]. The key criterion to meet this endpoint is a 4-point reduction in SLEDAI (qualified by no worsening in BILAG or Physician's Global Assessment). Hence, this criterion may be met by improvement in arthritis. The BILAG-2004 index is semiquantitative for each organ system assessed. For the musculoskeletal domain, BILAG A (the highest score) requires observed active synovitis in more than two joints with marked loss of functional range of movements. BILAG B is scored for tendonitis/tenosynovitis or active synovitis in more than one joint (observed or through history) with some loss of functional range of movement (or improving BILAG A disease). BILAG C is scored for inflammatory pain (e.g. with morning stiffness) without synovitis (or improving BILAG B disease). Pain without inflammatory symptoms (e.g. pain that clinically appears to be because of osteoarthritis) is scored as BILAG D, as are patients with no current symptoms. Analogous to the SRI from the SLEDAI, the based combined lupus assessment (BICLA) is a clinical trials endpoint derived principally from the BILAG. BICLA requires reduction of BILAG A or B scores by at least one grade (qualified by no worsening in other BILAG domains, SLEDAI, physician global VAS or treatment failure). Overall in the scoring of arthritis, all indices are strongly weighted by the detection of swollen joints.

Therefore, while clinical examination and laboratory markers are traditionally used to assess diseases their lack of specificity and sensitivity to change over time may limit their use in SLE. Histopathology, which is considered to be the diagnostic gold standard investigation for the presence of synovitis, does not play a large role here due to the invasive nature of obtaining tissue for analysis. Conventional radiography (CR) has been used for assessment of joint disease, but because it can only measure damage and not inflammation (as limited

soft tissue visualisation), it is becoming less beneficial as an outcome measure in the last few years. Magnetic resonance imaging (MRI), especially the gadolinium enhanced MRI, is widely considered to be one of the best imaging modalities for providing information about the synovium [4-6]. However, MRI is relatively expensive with limited access in many centres. In contrast, Ultrasound offers a feasible and inexpensive alternative for assessing synovial inflammation.

One of the most important, of recent insights, has been the observation from ultrasound studies that a large number of lupus patients with arthralgia had subclinical synovitis, despite the lower rates of clinical synovitis compared to other inflammatory arthritides. This is crucial for clinical practice and trials because existing clinical disease activity instruments are all heavily weighted by the presence of synovitis. Our group recently published a systematic review of these studies [7, 8].

The overall aim of my thesis is to improve the care of patients with musculoskeletal manifestations of Systemic lupus erythematosus.

Chapter 2: Literature Review

2.1 Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a chronic multi-system autoimmune condition with heterogeneity of laboratory and clinical manifestations ranging from mild musculoskeletal or cutaneous disease to potentially life-threatening renal, cardiac or central nervous system involvement. It is a lifetime disease with a relapsing and remitting course with variable severity [1, 9-11]. SLE predominantly affects women of childbearing age (female: male ratio of 9:1) with a peak incidence between the ages of 15 and 40. Nevertheless, SLE can affect all age groups [10, 12, 13].

2.1.1 *Epidemiology*

In Europe, the prevalence ranges between 20 to 50 cases per 100000 population, while much higher rates have been reported in Afro-Caribbean and Asian population [14]. In the UK, the prevalence of SLE had increased from 65 per 100 000 in 1999 to 97 per 100 000 in 2012 [15].

2.1.2 *Clinical features*

SLE is a multisystem disease with a heterogeneous spectrum of presentation and disease severity. The most common presentations are polyarthritis (joint pain and swelling), photosensitive skin rash, scaring or non-scaring alopecia, malar rash, and mucocutaneous lesions. In more severe cases, SLE can manifest with solid organ involvement such as nephritis, serositis (pleural and pericardial effusion), cardiac vasculitis, cerebritis and interstitial lung disease [16].

Classification criteria for SLE have been developed for the purpose of research and surveillance rather than clinical diagnosis. In 1971 the American College of Rheumatology (ACR) published classification criteria made of 11 criteria that occur in SLE, in order to be classified as SLE, at least four of them must be present serially or simultaneously during any interval of observation. These were revised in 1982 and 1997 [17, 18] (Table 2-1). There

are several issues with the ACR classification such as omitting hypocomplementemia, one of the most important characteristics for SLE. The criteria duplicated highly correlated cutaneous features such as photosensitivity and malar rash whilst excluding other common features as maculopapular rash. In 2012, the Systemic Lupus International Collaborating Clinics (SLICC) group revised ACR criteria to diagnose SLE, to require 4 of 17 criteria, with at least 1 of 11 clinical criteria and 1 of 6 immunological criteria being present; or biopsy-proven SLE nephritis in the presence of ANA or anti-dsDNA antibodies [19]. SLICC criteria (Table 2-1) demonstrate greater sensitivity (97% vs 83%, $p<0.0001$) but less specificity (84% vs 96%, $p<0.0001$) compared to the ACR criteria within validation cohort [20].

Table 2-1. ACR-97 and SLICC criteria

Criteria	1997 Revised ACR Criteria	SLICC 2012 Criteria
	Four out of 11 criteria are required for the classification of SLE	Four out of 17 criteria are needed, including 11 clinical and one of 6 immunological criteria. OR Biopsy-proven SLE nephritis in the presence of ANA or Anti-dsDNA antibodies are required to diagnose SLE
Mucocutaneous	**1- Malar rash:** Fixed erythema, flat or raised, sparing the nasolabial folds **2- Discoid rash:** Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scaring may occur in older lesions **3-Photosensitivity:** Skin rash resulted from unusual reaction to sunlight , by patients history or physician observation **4-Oral or nasal ulcer ulceration:** usually painless	1- **Acute cutaneous lupus** (ACLE) [lupus malar rash(do not count if malar discoid), bullous lupus, Toxic epidermal necrolysis variant of SLE, maculopapular lupus rash and photosensitive lupus rash in the absence of dermatomyositis OR **subacute cutaneous lupus** (SCLE) [non-indurated psoriasiform and/or annular polycyclic lesions that resolve without scarring] **2- Chronic cutaneous lupus (CCLE**) [classic discoid rash: localised above the neck or generalised above and below the neck, hypertrophic verrucous lupus, lupus panniculitis (prefunds), mucosal lupus, lupus erythematosus tumidus, chilblains lupus, discoid lupus/lichen planus overlap] **3- Non-scarring alopecia** Diffuse thinning or hair fragility with visible broken hairs in the absence of other causes 4. **Oral or nasal ulcers** :in the absence of other causes
Arthritis	**5- Non-erosive arthritis** involving 2 or more peripheral joints, charactarised by tenderness, swelling or effusion.	**5- Inflammatory synovitis** Involving ≥2 joints: characterised by swelling or effusion, OR Tenderness in 2 or more joints and ≥30 minutes of morning stiffness
Serositis	**6- Any of:** a. Pleuritis: convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion b. Pericarditis: documented by electrocardiogram or rub or evidence of pericardial effusion	**6- Any of** a. Typical pleurisy lasting >1 day, or pleural effusions or pleural rub b. Typical pericardial pain (pain with recumbency, improved by sitting forward) for >1 day, or pericardial effusion, or pericardial rub or pericarditis by electrocardiography in the absence of the other causes such as infection or uraemia
Renal	**7- Any of:** a. Persistent proteinuria >0.5 grams/day or >3+ on urine dipstick if quantitation not performed b. Cellular casts(maybe red cell, haemoglobin or granular tubular or mixed)	**7- Any of:** a. Urine protein- to- creatinine ratio (or 24 -h urine protein) representing ≥500 mg of protein/24 hour, or b. Red blood cell casts

Criteria	1997 Revised ACR Criteria	SLICC 2012 Criteria
Haematological	**8- Any of:** a. **Haemolytic anaemia with reticulocytosis** b. **Lymphopenia:** <1500/mm3 c.**Thrombocytopenia**: <100 000/mm3 in the absence of offending drugs	**8- Haemolytic anaemia** **9-Leucopoenia** (<4000/mm3), OR **lymphopenia** (<1000/mm3) of at least once in the absence of other known causes **10-Thrombocytopenia** (<100 000/mm3) of at least once in the absence of other known causes.
Neurological	**9- Any of:** Seizures: in the absence of offending drugs or known metabolic derangements b. Psychosis: in the absence of offending drugs or known metabolic derangements	**11- Any of:** a. Seizures b. Psychosis c. Mononeuritis multiplex(in the absence of other known causes as primary vasculitis) d. Myelitis e. Peripheral or cranial neuropathy (in the absence of other known causes as diabetes, primary vasculitis or infection) f. Cerebritis (acute confessional state) in the absence of other known causes as toxic, metabolic or drugs
Immunological	**10- Any of:** a. **Anti-DNA:** antibody to native DNA in abnormal titre b. **Anti-Sm:** presence of antibody to Sm nuclear antigen c. Positive finding of **anti-phospholipid antibodies** based on: (i) an abnormal serum concentration **of IgG or IgM anti-cardiolipin antibodies**, (ii) a positive test result for **SLE anti-coagulant** or (iii) a false-positive serological test for **syphilis** known to be positive for ≥6 months and confirmed by *Treponema pallidum* immobilisation or fluorescent Treponemal antibody absorption test	**12- Anti-dsDNA** above laboratory reference range (or 2-fold the reference range if tested by enzyme –linked immunosorbent assay ELISA) **13- Anti-Sm** presence of antibody to Sm nuclear antigen **14**- **Anti-phospholipid antibody** SLE anti-coagulant, false-positive test for syphilis **15- Anti-cardiolipin** (at least twice normal or medium–high titre), or anti-β2 glycoprotein 1 **16. Low complement:** low C3, or low C4, or low CH50 **17**- **Direct Coombs test** in the absence of haemolytic anaemia
Antinuclear antibody(ANA)	**11- Abnormal titre of ANA by** immunofluorescence or an equivalent assay at any time and in the absence of drugs which my induce lupus	**18- ANA** above laboratory reference range

2.1.3 *Pathogenesis of SLE*

No single entity can be identified as the dominant factor in the pathogenesis of SLE. This condition is a multifactorial disease with genetic susceptibility and environmental factors resulting in innate and adaptive immune system imbalance. In addition to the inadequate clearance of apoptotic cells, increased cytokine production, and aberrant B- cell immunity and T-cell signalling also play a role here [21].

The central pathogenic feature is the production of autoantibodies in particular against nuclear antigen, resulting in immune complex deposition inflammation and end organ damage [10, 13, 22]. The characteristic feature of SLE is the deposition of immune complexes within the tissue, results in activation of the complement system with the recruitment of inflammatory cells, and consequent vasculopathy [13, 16].

Aberrant immune response has a significant role in the development of SLE, this happens through both tissue injury via release of inflammatory cytokines and through aberrant activation of autoreactive T and B cells. Consequently, production of autoantibody and end-organ injury [23].

The first step in the development of SLE is the breakdown of self-tolerance. Deficiency in the clearance of apoptotic cells leads to abundance of nucleic acid remnants. These activate the TLR7 and TLR9, expressed by plasmacytoid dendritic cells (pDCs) leading to excessive production of inflammatory cytokines including IFN-alpha (IFN-α). IFN-α activates several components of the immune system including myeloid dendritic cells (mDCs). Once activated, mDCs present self-antigens and other proteins to T- and B-cells leading to cell proliferation, maturation, differentiation and survival, and excess autoantibody and cytokine production.

The second step in the development of SLE pathology is the production of autoantibodies. Initiated by ANA presentation on Dendritic cells (DC), antigen specific T cells.

T-cell receptor interacts with MHC on antigen presenting cells and triggers the T-cell

response These stimulate T cell in addition to co-stimulatory molecules such as CD28:B7 and CD40:CD40 ligands, these help activate B-cells. Thus, autoreactive T-cells provide help to B-cells which subsequently produce a large amount of autoantibodies.

In healthy individuals, immune complexes are cleared by Fc and complement receptors [24] However in SLE, genetic variations in FcR genes and the C3bi receptor gene (ITGAM) [25, 26] may impair the clearing of immune complexes, which then deposit and cause tissue injury at sites such as the skin and kidney. Immune complex-associated inflammation can also occur activation of macrophages and neutrophils via surface Fc-receptors which bind IgG. Finally, the production of pro-inflammatory and pro-fibrotic cytokines including IL-4 and tissue growth factor-beta (TGF-β) lead to irreversible tissue damage or scarring. Eventually, as these immune elements remain dysregulated in SLE, these lead to more tissue damage and cell death, perpetuating the cycle of inflammation [25].

2.1 Pathogenesis of SLE arthritis

Genetic susceptibility plays a central role in this process. Many studies have attempted to identify candidate susceptibility genes, which could be responsible for the development of SLE arthritis. However, despite the identification of several possible genes, to date, no clear explanation of the mechanisms of these associations has been developed. A study conducted by Warchol et al. demonstrated a significant correlation between the development of arthritis and the ITGAM (Integrin alpha M) gene [27]. De Azevedo Silva et al. showed a relationship between arthritis and polymorphism within the Vitamin D Receptor (VDR). They demonstrated that Vitamin D affects the differentiation of dendritic cells, and in turn inhibits B cell proliferation, inhibiting Th1 immune response and upregulation of regulatory T cells [28]. Low Vitamin D level is a common finding within SLE cohorts [29]. Correlation between C4 and the ACP5 (Acid Phosphatase 5) variant has also been associated with the development of SLE arthritis [30, 31]. Low FCGR3A (Fc fragment of IgG receptor III-a) and FCGR2B (Low affinity immunoglobulin gamma Fc region receptor II-b) genes were highly associated with the development of arthritis in Taiwanese SLE patients [32, 33].

In several studies, the presence of high serum IFN alpha level is associated with the development of SLE and correlates with increased severity and activity. The gene expression pattern of IFN is called IFN signature [34]. MIR146a (MicroRNA 146a) has some regulatory effects on the IFN pathway and the under-expression of this microRNA has been demonstrated in SLE patients with arthritis [34]. SNPrs15866 of STK17A gene has also demonstrated a relationship with SLE arthritis. The STK17A gene encodes a nuclear protein known as DRAK1 (DAP protein kinase related apoptosis-inducing kinase 1). DRAK1 plays a major role in the regulation of nuclear and apoptotic cellular processes, including DNA damage repair. UV-light exposure and certain medications can activate the STK17A polymorphism which explains its possible role in the initiation of SLE arthritis [35].

Eilersten et al in a cross-sectional study comparing the level of pro-inflammatory cytokines between SLE, RA patients and a group of healthy controls. They found high levels of IL-6, IL-8, IL-1 beta and TNF expression in the SLE and RA patients. Notably, patients with SLE with ongoing inflammatory arthritis had substantially higher levels of IL-6 [36]. Ball et al. confirmed this in 2014. They showed correlations between IL-6 levels and ultrasound findings of active arthritis(Grey scale and Power Doppler) in SLE patients with JA [37].

At a molecular level, synovial mediator expression studies in SLE patients demonstrate a distinct appearance compared to osteoarthritis and RA. SLE synovium has marked upregulation of type I IFN-stimulated genes and downregulation of extracellular matrix homeostasis [38]. The stratification of SLE according to type I IFN status is increasingly important as this may predict response to a range of therapies. However, the role of type I interferons in arthritis is complex. Interferon (IFN)-alpha expression, primarily produced by circulating plasmacytoid dendritic cells and monocytes is generally associated with more severe disease in SLE [39]. Interestingly, although interferon expression is related to overall disease activity and individual organ involvement such as mucocutaneous disease, it has not clearly been associated with arthritis [40]. Synoviocytes and fibroblasts produce IFN-b and this has been shown in laboratory models to have regulatory roles in terms of down-regulatory

effects on Tumour Necrotizing Factor and up regulatory effect on Tumour Growth Factor- b, Interleukin (IL)-10, and IL1ra [41-44]. Meanwhile, an interferon regulatory factor 5 risk haplotype for SLE has been associated with non-erosive rheumatoid factor-negative RA suggesting an overlapping role for interferon-mediated pathogenesis [45]. Understanding the role of type I interferons in SLE is of renewed interest as therapies that target this pathway have demonstrated efficacy for arthritis-specific outcomes in phase III trials when targeting either (IFN)-alpha alone or the interferon receptor that is shared by IFN-a and IFN-b [46, 47].

2.2 Aetiology:

The exact cause of SLE remains vague. This condition results from interaction between different factors among various genetic, epigenetic, hormonal and environmental factors is probably involved [48].

2.2.1.1 Genetic factors

Genetic susceptibility plays a key role in the development of SLE. This can be seen in the concordance of SLE in identical twins, the large number of SLE among first degree relatives and the increased risk of developing the disease in siblings of SLE patients reflects a polygenic inheritance of the disease Homozygous deficiency in the early complements system has been associated with a high risk of developing SLE. In addition, the concordance rate in monozygotic twins is up to 57% [49, 50]. The first degree relatives of SLE patients have a 17-fold increased risk of developing the disease when compared with general population [51, 52]. Of the genetic elements, the genes of the major histocompatibility (MHC) have been extensively studies for their role to SLE development. Studies revealed that the susceptibility to SLE involves human leucocyte antigen (HLA) class II gene polymorphism. An association was found between HLA DR2 and DR3 with a relative risk for the development of the disease of approximately two to five. The HLA class II genes have been associated with the high level of anti-dsDNA, anti-nRNP, anti-Ro, anti-La and anti-Sm antibodies. Genetic alterations in Mannose Binding Protein,

TNFα, the T-cell receptor, IL-6, Complement Receptor 1, immunoglobulin Gm and Km allotypes, FcγRIIA and FcγRIIIA (both IgG Fc receptors), and heat shock protein 70 are also known risk factors [13].

Most single-nucleotide polymorphisms (SNPs) linked to SLE are components of non-coding DNA regions of immune response-related genes [53, 54]. Some genes are specific to SLE. Certain SNPs associated with SLE have been identified to contribute to aberrant dendritic cell function and interferon (IFN) signalling (TREX1 and STAT4); whilst others are linked to dysfunction of immune-complex processing and innate immunity such as impaired interleukin (IL) expression (C1QA, ITGAM); T cell function and signalling (STAT4 and PTPN22); cell cycle, apoptosis and cellular metabolism (CASP10); and transcriptional regulation (MECP2) in SLE [55].

SLE is associated with the inherited deficiency of complement components C1q, C1r/s, C2, and C4. This decrease in complement activity could promote the susceptibility to the disease by impairing the neutralisation and clearance of self and foreign antigens. This accumulation of antigen overwhelms the clearance capacity of the immune system [13].

2.2.1.2 Epigenetic effects

Epigenetic effects such as DNA methylation, post-translational histone modifications and micro ribonucleic acids (miRNAs), either genetically determined or environmentally induced may influence the risk of SLE [56]. The role of epigenetics is supported by the discordance seen in identical twins who are discordant for SLE [57]. The most well-understood type of epigenetic factor is DNA methylation, which affects specific genes and variation in acetylation of histones, therefore, effects transcription into protein. DNA methylation plays a key role in a variety of human processes. Abnormal methylation has been associated with development of SLE [58] miRNAs are important in both adaptive and innate immunity by controlling the differentiation of different immune cell subsets such as B-cells, T-cells and their immunological functions [59, 60]. Aberrantly expressed miRNAs have been observed in different cell types, tissues and play an important role in the progression of SLE [61].

2.2.1.3 Nuclear antibody spectrum and SLE

The presence of Anti-nuclear antibody (ANA) is one of the immunological criteria present in both SLE classifications (Table 2-1). Negative ANA test (titer less than 1/160) makes the diagnosis of SLE unlikely. Hence it represents an essential screening tool for the disease. On the other hand, positive ANA even with a high titer is not specific for SLE as it is also found in a variety of other conditions including other connective tissue diseases (CTDs), virus infections, hepatic and haematological diseases. In addition, up to 5% of healthy individuals in the western word are ANA positive with the majority of them never having any symptoms of CTD. Various types of SLE-specific ANA anti-bodies are summarized in (Table 2-2) [55].

Table 2-2. ANA antibodies associated with SLE

ANA	Prevalence	Sensitivity	Specificity	Clinical features
Anti-dsDNA	43-92%	5-54%	89-99%	Related to disease activity
Anti-nucleosome	60-62%	52-61%	88-96%	Related to disease activity
Anti-Sm	15-56%	10-55%	98-100%	Highly specific for SLE
AntiC1q	4-60%	28%	92%	Associated with lupus nephritis
Anti-Ribosomal P	12-60%	36%	97-100%	Neuropsychiatric Lupus
Anti-Ro/SSa	36-64%	-	-	Congenital heart block-Cutaneous SLE
Anti-La/SSb	8-34%	26%	98%	Same as Anti-Ro, less frequent
Anti-RNP	23-49%	8-69%	25-82%	Mixed CTD
Anti-histone	50-80% >90% in drug induce SLE.	-	-	Drug induce lupus

2.2.1.4 Hormonal factors:

The prototypical patient with SLE is a female of childbearing age [62] suggesting a pathogenic role of oestrogen hormone [13]. This is supported by evidence that SLE patients have abnormal oestrogen metabolism with high level of expression of 16α-hydroxyestrone (16α – OH-E1) and low level of expression of testosterone, dihydrotestosterone, dehydroepiandrosterone (DHEA), and dehydroepiandrosterone sulfate [63-65]. In contrast, high serum androgens levels are associated with low SLE disease activity [63]. Oestrogen stimulates thymocytes, CD8+ and CD4+ T-cells, B-cells, macrophages leading to the release of some types of cytokines such as (IL-1) [66]. Oestrogen also reduces apoptotic activity in self-reactive B-cells, thus promoting the maturation of autoreactive B-cells with high affinity for anti-dsDNA [67]. It has been reported that women who had early

menarche or those receiving oestrogen-containing treatment such as oral contraceptives or postmenopausal hormone replacement therapy had a significantly increased risk for SLE (HR of 1.5 to 2.1) [68]. In contrast, male patients with SLE have lower testosterone levels compared to those without the disease [69].

2.2.1.5 Environmental factors

Environmental factors are known to trigger SLE and disease activity. Ultraviolet (UV) light and smoking increase the risk of SLE development through unknown mechanisms. Exposure to UV light can exacerbate cutaneous SLE erythematosus and increase the risk of a flare. This causes aberrant apoptosis of keratinocytes and contributes to the accumulation of apoptotic cells in the skin of patients with SLE [70]. Apoptotic cells that fail to be cleared by phagocytes undergo secondary necrosis and subsequently releasing inflammatory mediators including IL-1, IL-3, IL-6, granulocyte macrophage colony-stimulating factor (GM-CSF), IFNs and TNF, thereby stimulating B-cells to make more antibodies [71]. Other factors include exposure to silica dust, petroleum and organic solvents [21]. Infectious agents, drugs and dietary factors have the ability to modulate the immune response and potentiate progression to SLE in individual who considered to be 'at risk' [13]. It is known that viral infections, such as Epstein-Barr virus (EBV) are linked to the initiation and exacerbation of SLE. Studies on EBV in SLE patients found high antibody titers of anti-EBV antibodies and increased viral load. These individuals also make antibodies to protein regions of retroviruses which are homologous to nuclear antigens [72].

There are many reports about drug-induced lupus (DIL). The implicated drugs are mainly those that are metabolized by acetylation such as procainamide and hydralazine, especially in people who are genetically slow acetylator phenotype [73].

2.2.2 *Management of SLE*

Although considerable progress in SLE prognosis and management has been made in the last century, successful treatment of moderate to severe SLE remains unsatisfactory when

compared with rheumatoid arthritis management. Potential reasons for this include paucity of randomized controlled trials of SLE treatment and the lack of the uniformity in SLE research inclusion criteria. The heterogeneity and complexity of SLE are major factors that cause difficulty in identifying the best treatment for it [74, 75]. The goals of successful SLE management care are: low disease activity, avoidance of organ damage and minimising systemic corticosteroid exposure [75].

2.2.3 *Non-Steroidal Anti Inflammatory Drugs*

Nonsteroidal anti-inflammatory drugs (NSAID) have analgesic, antipyretic and anti-inflammatory properties through their inhibitory effect on cyclo-oxygenase1 (COX-1) and (COX-2). NSAIDs are commonly used for symptomatic relief of arthralgia, mild arthritis, myalgia and fever in patients with SLE. However, there is a lack of strong evidence to support the safety or efficacy of NSAIDs in clinical trials. They can be used for short periods of time to minimise their side effect profiles. This includes interstitial nephritis, renal impairment, fluid retention, peptic ulceration and increased risk of ischemic heart disease [16, 76].

2.2.4 *Glucocorticoids*

Glucocorticoids are potent immunosuppressant drugs that induce the formation of anti-inflammatory cytokines (IL10, IL1Ra) and reduce the formation of adhesion molecules and inflammatory cytokines (IL2, IL6 and tumour necrosis factor). There are additional immunosuppressant effects which include the inhibition of antigen presentation and the synthesis of COX-2 and nitric oxide synthase. Despite their toxic side effects (including osteoporosis, diabetes mellitus, increased infection risk and cardiovascular disease), glucocorticoids tend to produce a significant improvement in severe autoimmune disease. Glucocorticoids are the mainstay of SLE treatment in the acute phase of the disease due to the rapid onset of its anti-inflammatory effects [77, 78]. The preference is for glucocorticoids to be prescribed at the lowest possible dose for the shortest period of time as the cumulative exposure is directly linked with their side effect profile [16]. They can be given in topical form for inflammatory cutaneous systemic lupus, as an intra articular preparation in active localised

synovitis, or alternatively as intramuscular and intravenous preparations [76].

2.2.5 *Hydroxychloroquine and other antimalarial medications*

Hydroxychloroquine has immunomodulatory properties without immunosuppressive effects. It is recommended and licensed for use in SLE patients unless there are contraindications [74]. The pharmacodynamics properties of the drug are based on alteration of lysosomal pH which leads to decreased cytokine and reduced prostaglandin production. Hydroxychloroquine blocks toll-like receptors on PDCs, by decreasing TLR signaling, this reduces the activation of DC and the inflammatory process. TLR 9 recognizes DNA-containing immune complexes and leads to the production of IFN and causes the DC to mature and present antigen to T cells, therefore reducing anti-DNA auto-inflammatory process. The starting dose is 200-400mg daily. Its use in SLE has been supported by a randomized control trial conducted by Williams et al. where significant improvement was noticed in the patients with hydroxychloroquine compared to placebo [78]. For many years hydroxychloroquine was the primary treatment for CLE and serological abnormalities. A phase III double blinded-clinical trial conducted in Japan for 103 patients with CLE were randomised to receive hydroxychloroquine or placebo. They reported that the investigator's global assessment showed a large number of patients who received hydroxychloroquine either "improved" or "remarkably improved" in terms of their disease activity (51.4% versus 8.7% in the placebo group [P=0.0002 between groups]) [79]. Evidence also exists that hydroxychloroquine has additional benefits in improving overall survival in SLE [80]. Recently, it has been shown to have cardio protective effects by reducing the level of total cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides (TG) and increasing high-density lipoprotein (HDL) cholesterol levels. Patients on hydroxychloroquine require annual ophthalmology follow up to screen for retinal toxicity (known as plaquenil maculopathy or Bulls eye maculopathy) which can lead to irreversible loss of central vision [76, 81, 82].

2.2.6 *Conventional Disease Modifying Anti-Rheumatic Drugs (cDMARDs)*

In the event that SLE patients require glucocorticoids at a dose of 5-7.5 mg/day or equivalent, which cannot be reduced or discontinued, the EULAR recommendations are to add in steroid-sparing agents [83]. These agents are typically used for induction of remission when glucocorticoids are contraindicated or in more severe cases of arthritis [78].

2.2.6.1 Methotrexate

Methotrexate is an anti-folate drug with anti-inflammatory and immunosuppressive properties. It inhibits DNA synthesis and is the most commonly prescribed agents for rheumatoid and psoriatic arthritis treatment [84]. Several clinical trials support its use as a potentially effective agent in the management of SLE arthritis and this is supported by positive outcomes in many clinical trials [84-86]. It can be considered as the leading steroid-sparing agent in SLE patients with articular presentation [84].

2.2.6.2 Azathioprine

Azathioprine is metabolized to 6 mercaptopurine and has immunosuppressant effects through suppression of xanthylic and adenylic acids synthesis. It is one of the steroid-sparing agents which has shown its effectiveness in SLE patients who have central nervous system or renal involvement. It is effective and safe to be prescribed during pregnancy [81, 87]. The main adverse effects are gastrointestinal manifestations which include nausea, vomiting, diarrhoea and elevation of liver enzymes. It can also cause reversible bone marrow suppression. Prior to commencing azathioprine, Thiopurine Methyl Transferase (TPMT) enzyme levels are checked. Patients with a low level of the TPMT enzyme are prone to leukopenia due to drug toxicity as they lack sufficient levels to be able to adequately clear azathioprine from their bodies [76].

2.2.6.3 Mycophenolate Mofetil

Mycophenolate Mofetil (MMF) mainly acts on inosine monophosphate dehydrogenase which inhibits B-and T-lymphocyte proliferation. It has been used in SLE arthritis with positive

outcomes [88, 89]. The ALMS (Aspreva Lupus Management Study) showed that MMF was successful in the induction and maintenance of remission as well as prevention of flares in SLE nephritis. The study concluded that the combination of MMF with corticosteroid is comparable to cyclophosphamide with corticosteroid in the induction and maintenance of remission in SLE nephritis [90].

2.2.6.4 Cyclophosphamide

Cyclophosphamide prevents the division of cells by cross-linking DNA and suppressing DNA synthesis. It can be given intravenously or orally, and clinical trials suggested that intermittent IV pulse therapy is less toxic and more efficacious. It has become the treatment of choice for the induction of remission of severe SLE nephritis with the added benefit of preventing progression to end-stage renal failure [91]. Additionally, it can induce remission in severe neurological manifestations such as SLE cerebritis or neuropathy. The side effects of cyclophosphamide include bone marrow suppression, gastrointestinal upset and premature ovarian failure. There is also an increased risk of opportunistic infections, haematological malignancies and bladder cancer. It is not safe to be given in pregnancy and should be discontinued at least three months before conception [76].

2.2.7 *B cell depleting agents*

B-cells have a central role in the pathogenesis of several autoimmune diseases such as RA and SLE through their maturation into antibody secreting plasma cells, production of pro-inflammatory cytokines, antigen presentation and supporting T-cells[92]. Inhibiting B-cells using antibodies against CD19 and CD20 can potentially modulate this process. Anti-CD20 mAbs can be subdivided into type I or type 2 according to their ability to induce the reorganisation of CD20 molecules into lipid rafts upon binding. Type1 mAbs induce translocation of CD20 into lipid rafts and efficiently activate the classical pathway of the complement system. Examples include rituximab, ofatumumab and ocrelizumab. Conversely, type 2 mAb such as obinutuzumab poorly activates complement but directly induces cell death upon binding to CD20 without cross-linking by with secondary antibodies. Both types of mAbs

are capable of inducing antibody dependent cell-mediated cytotoxicity (ADCC) in the presence of effector cells [93].

2.2.7.1 Rituximab

Rituximab is an anti-CD20 chimeric mAbs that has been used successfully in many autoimmune diseases in which B-cells are implicated [94-97]. Rituximab kills B-cells by different mechanisms: 1- ADCC in the presence of effector cells, 2-complement activation resulting in complement-dependent cytotoxicity (CDC) and, 3-cross-linking of multiple CD20 molecules, leading to cell death via induction of apoptosis [93].

It was approved for the treatment of B-cell lymphoma in 1997. Several recent double-blind placebo controlled trials of rituximab in RA have shown its effectiveness and safety [98, 99]. However, the pivotal trials of rituximab in SLE have failed to reach their end points[81]. The problems with these trials is discussed in more detail in 2.15.

Nevertheless, the drug is commonly used based on open label data. Rituximab was first used in an open uncontrolled study by Isenberg et al. It was shown to improve both clinical and laboratory manifestations in patients with refractory SLE [100, 101].

2.2.7.2 Belimumab

Belimumab is the only licenced biological therapy for SLE. It is a fully humanised mAb that specifically binds to and neutralises B-cell Activating Factor (BAFF). This decreases the life span of CD20+ B-cells, reducing expression of both B-lymphocyte stimulator (BLyS)/BAFF and positive feedback for B-cell survival and anti-dsDNA expression. There are two cytokines responsible for B-cell survival, maturation and differentiation BAFF and its homologue: A PRoliferation-Inducing Ligand (APRIL). They bind to three receptors that are expressed on B-cells at different stages, thereby activating their own signalling pathways: i-BAFF receptor (BAFF-R) binds BAFF strongly; ii- B-cell maturation antigen (BCMA) binds APRIL and iii-TNF receptor superfamily member 13b (TACI) binds both BAFF and APRIL. Approved for the treatment of SLE in 2012 on the indication of severe disease despite having maximum

treatment or the requirement for very high glucocorticoid dose

Two Randomised control trial BLISS 52 and BLISS 76 assessed the efficacy of belimumab over placebo in active SLE patients. Both studies reached their primary endpoints. The endpoints were (a) improvement in the Systemic Lupus Erythematosus Responder Index (SRI) at week 52 (which is defined as reduction ≥4 points in SELENA-SLEDAI score (b) no new British Isles Lupus Assessment Group [BILAG A] organ domain score and no worsening in Physician's Global Assessment [PGA] score comparing to baseline [67, 97, 98, 102, 103]. These outcome measures and potential trial design issues are also discussed further below.

2.2.7.3 Epratuzumab

Epratuzumab is a fully humanised mAb targeting CD22. It induces complete depletion of activated B-cells without influence on T-cells or serum levels immunoglobulins [76]. Many studies have shown that epratuzumab reduces total BILAG score and glucocorticoid requirements [104, 105].

2.2.7.4 Ofatumumab

Ofatumumamb is a fully human anti-CD20 mAb which binds to a membrane-proximal epitope of the CD20 molecules (targets a different epitope than rituximab). It is used for resistant chronic lymphoblastic leukaemia and with evidence for efficacy in RA, but no study has been done in SLE [106].

2.2.7.5 Ocrelizumab

Ocrelizumab is a humanized monoclonal antibody that targets CD20+ B-cells. In-vitro ocrelizumab has demonstrated enhanced ADCC and reduced complement-dependent cytotoxicity when compared with rituximab [107]. It met their endpoints; American College of Rheumatology 20% improvement criteria (ACR 20%) in RA clinical trials[107, 108]. But this development and its use was stopped due to some safety issues such as increasing the risk of opportunistic infections[109].

2.2.8 *Interferon blockade*

Interferon (IFN) is a family of cytokines that are typically secreted by cells in response to exposure to a pathogen (viruses) or nucleic acids from increased apoptosis. There are three types of the INFs: Type I, Type II and Type III IFN that differ according to molecular subtype and IFN receptor binding. Type I IFNs (IFN-I) is the largest family and consists of the IFN-α and IFN-β molecular subtypes which bind to the IFN-α receptor (IFNAR). Dysregulation in the IFN pathway is considered to play an essential role in the development and activity of SLE[110]. Many studies have shown that high IFN-α expression correlated with both increased activity and severity of SLE [111, 112]. The increased expression levels of IFN regulated genes (called the IFN signature), correlates closely with the presence of auto-antibodies and SLE disease activity [113]. Supersession of this pathway is the target of many therapeutic agents for SLE.

Sifalimumab is a fully human IgG1k monoclonal antibody that inhibits Type I IFN-α. Promising results were found in a phase IIb randomized, double-blind, placebo-controlled study in subjects with moderate to severe SLE. Patients who received sifalumumab met the primary end points in comparison with the placebo group [114]. The details of this study are discussed in 2.23.1.

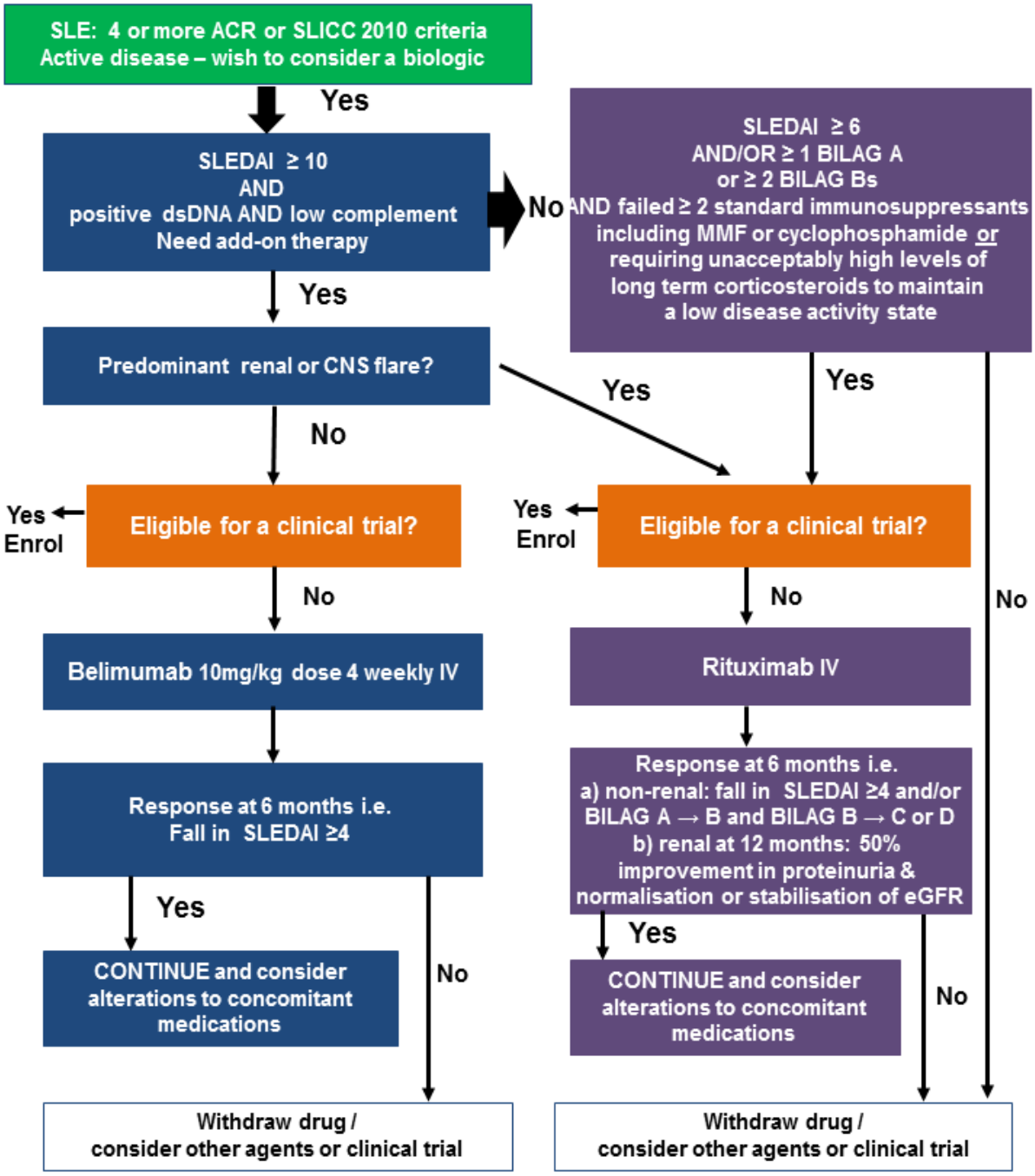
Rontalizumab is a humanized IgG1 monoclonal antibody against IFN-α. There were acceptable results from a phase I dose-escalating study [115]. A Phase II study of the efficacy and safety of rontalizumab showed a failure to meet the primary and secondary endpoints. However, it reported an improvement in disease control based on a reduction in flares and steroid use [116].

Anifrolumab is a fully human IgG1κ monoclonal antibody directed against subunit 1 of the type I IFN Receptor (IFNAR1). It has been studied in a phase II, open-label, dose-escalation study in Japanese SLE patients [117]. The results of a phase II efficacy and safety study in adults with moderate to severe active chronic SLE with inadequate response to standard treatment illustrated reduced disease activity in anifrolumab recipient compared with placebo [118]. The details are discussed in 2.23.2.

2.3 Criteria for biologic therapy for SLE in the UK

The current criteria for the use of belimumab and rituximab in SLE are shown in (Figure 2-1). For patients with predominant musculoskeletalinvolvement these will require at least BILAG B or SLEDAI MSK points more than four, therefore they will need clinical synovitis. For belimumab, to achieve 10 points on the SLEDAI the patient will need four points for clinical synovitis, four points for the required dsDNA antibodies and complement, and two points elsewhere in the score (e.g., mouth ulcers or alopecia). For rituximab, patients require either BILAG B (moderate synovitis) as well as one other BILAG B in another domain, or BILAG A (severe synovitis) alone. Hence, it is not possible for patients to receive biologic therapy for musculoskeletal SLE unless they have at least moderate synovitis.

Figure 2-1. Criteria for Biological therapy in the UK [119, 120]



ACR: American College of Rheumatology, BILAG: British Isles Lupus Assessment Group, CNS: Central Nervous System SLEDAI: Systemic Lupus Erythematosus Activity Index, SLICC: Systemic Lupus International Collaborating Clinics.

2.4 Musculoskeletal SLE

Musculoskeletal manifestations are among the most common features of SLE both in initial diagnosis and in long-term management. The control of musculoskeletal SLE symptoms is critical as they are crucial to the overall patient outcome as well as the influential in the development of new therapies [7]. Articular involvement is mainly characterised by transient, migratory arthralgia and arthritis. The spectrum of musculoskeletal conditions also includes: myositis, tenosynovitis, tendon rupture, tendinitis or non-inflammatory presentations such as avascular necrosis of the bone and fibromyalgia [121]. In a minority of cases deforming and/or erosive arthropathy, respectively named Jaccoud's arthropathy(JA) and Rhupus syndrome can be found [122]. Musculoskeletal SLE is the theme of this thesis.

2.5 Importance of Musculoskeletal SLE

Musculoskeletal manifestations of SLE are the first presenting symptom in up to 50% of patients with SLE and affect up to 95% of patients during the clinical course of the disease [123, 124] . Although other manifestations may be more critical in terms of risk of organ failure and early mortality, musculoskeletal manifestations are the key determinant of disease impact in this group of patients. Apart from fatigue, the most frequently reported difficult symptom of SLE is pain (50%) and musculoskeletal (46%) and these symptoms were most strongly related to reduced health-related quality of life [125]. In a systematic review, only 47% of SLE patients reported to be engaged in full-time employment and 34% reported work disability[126]. Arthralgia was individually the only symptoms to be significantly associated with work disability, with odds ratio (OR) of 2.41 [95% confidence interval (CI)1.53–3.79] [127]. By comparison, overall disease activity as measured by the systemic lupus erythematosus disease activity index (SLEDAI) showed no association with work disability, and when measured by Systemic Lupus Activity Measure (SLAM) had only a modest association (OR 1.12, 95% CI 1.03–1.21). Age, household income, and fibromyalgia were most strongly associated with work disability. In a longitudinal follow-up, 34 % of patients with musculoskeletal manifestations discontinued their involvement in the workforce after a median

of four years [128]. Arthralgia is, therefore demonstrated to be one of the most important modifiable factors in disability in SLE patients. Musculoskeletal manifestations of SLE are frequently treated with glucocorticoids and NSAIDs, and both have an association with an increasing rate of long-term cardiovascular complications. A recent French study found that cardiovascular disease is the greatest cause of mortality in SLE [129], and in a 2016 systematic review cardiovascular diseases were most strongly associated with increased standardized mortality ratios in SLE after renal disease and infection[130].

Interestingly, cluster analysis of Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index domains found low level damage, musculoskeletal damage, and cardiovascular damage, to be associated with death rates of 3.7,10.8, and 20.5%, respectively[131]. Regarding therapeutics: the majority of non-renal SLE patients qualify for clinical trials and biologic therapy because of activity in skin and musculoskeletal systems. For example, in the ILLUMINATE-1 phase III trial of tabalumab (anti BAFF), 78.8–83.5% of patients had activity in the musculoskeletal system in each arm. Only Skin involvement was more common than musculoskeletal activity: and the proportions of patients with activity in other organs was far smaller: the next largest clinical manifestation was haematological – approximately 11% of patients [132]. In the UK BILAG registry data, 31% of all renal and non-renal SLE patients treated with a biologic in the UK received it for musculoskeletal disease [133].

2.6 Subtypes of SLE Arthritis

2.6.1 *Jaccoud's Arthropathy*

Jaccoud's arthropathy (JA) was first described as a non-erosive arthropathy with reversible deformities in association with rheumatic fever. An identical phenotype was noted in patients with SLE in 1975 [134]. JA may also occur in other connective tissue diseases, although, this appearance is frequently cited as being pathognomonic for SLE in the textbooks. It is in fact, quite an uncommon characteristic of SLE. The prevalence of JA in SLE range from 2.8 to 3.5% in the registry database of the last decade [135, 136].

2.6.2 *Rhupus*

Approximately 5% of SLE patients are estimated to present with a combined RA/SLE clinical syndrome referred to as 'Rhupus'. These patients meet classification criteria for both RA and SLE, which presents as erosive arthritis with identical radiographic appearance to RA, and often in association with rheumatoid factor and anticitrullinated peptide antibodies. The pathogenesis of rhupus is thought to be more typical of RA [137, 138]. A recent study compared features of SLE arthritis among children and adults. Although chronic polyarthritis tended to be more common and severe in children, rates of JA and rhupus did not differ between the two groups [139].

2.6.3 *Non-deforming Non-erosive Arthritis*

The vast majority of patients with SLE arthritis are described as non-deforming non-erosive (NDNE) arthritis. Although these patients have similar inflammatory features to other inflammatory arthritidis , such as symmetrical small joint distribution and morning stiffness, clinically detectable synovitis is present in only a small number of patients [7]. Non Inflammatory musculoskeletal symptoms in SLE

A great majority of SLE patients present with nonspecific, non-inflammatory clinical features which are difficult to distinguish from the inflammatory manifestations [121].

2.6.4 *Fibromyalgia*

Fibromyalgia (FM) is a widespread chronic musculoskeletal pain disorder affecting 2-3% of general population. It is widely defined according to ACR criteria as tenderness on palpation of at least 11/18 bodily points for a minimum three month period [140-142]. It is associated with fatigue and somatic symptoms such as poor sleep, mood and neurological disturbances[143]. There are no objective or laboratory features to evaluate FM. It is difficult to differentiate FM from SLE, and their concomitant prevalence is approximately 20%, which means FM is more common in SLE patients than in the general population [144]. There are many shared symptoms between SLE and Fibromyalgia and this may lead to

misinterpretation, misdiagnosis and over treatment[145]. Di Franco et al. studied patients with different rheumatological inflammatory diseases and fibromyalgia and they detected a substantial proportion of patients with FM had been misdiagnosed as having connective tissue disease, including SLE [142]. Wallace and colleagues studied 44 female patients who had been referred to the rheumatology clinic because of positive ANA and found after six months that 19/44(43%) met the ACR criteria for SLE while 14/44 (32%) fulfilled the ACR criteria for FM [146]. Gladman et al. studied 119 patients with SLE. They reported that the prevalence of fibromyalgia was 21% and there was no relation to either the overall scores or any of the components of SLEDAI or Damage Index but there was a strong negative correlation with all eight domains of the Short Form 36(SF-36) [147].

2.6.5 *Avascular Necrosis*

Systemic lupus erythematosus itself and the drugs used to treat it interfere with the blood supply to the bone and initiate the process of necrosis. Osteonecrosis is a painful condition that interferes with the quality of life of patients in terms of pain and impaired mobility[148]. There are many factors beyond those mentioned that may cause osteonecrosis; long duration and large doses of steroid use, Raynaud phenomenon, vasculitis, and antiphospholipid syndrome [149]. The prevalence of osteonecrosis varies between 4.6% and 40% [150].

2.6.6 *Osteoporosis*

Low bone density, osteoporosis and fragility fractures are common in SLE. Osteopenia is found in 4% to 74% and Osteoporosis in approximately 3% to 48% of patients with SLE. Risk factors include immobility, chronic inflammation, and vitamin D deficiency often due to lack of sun exposure and steroid treatment leads to decrease bone formation [151].

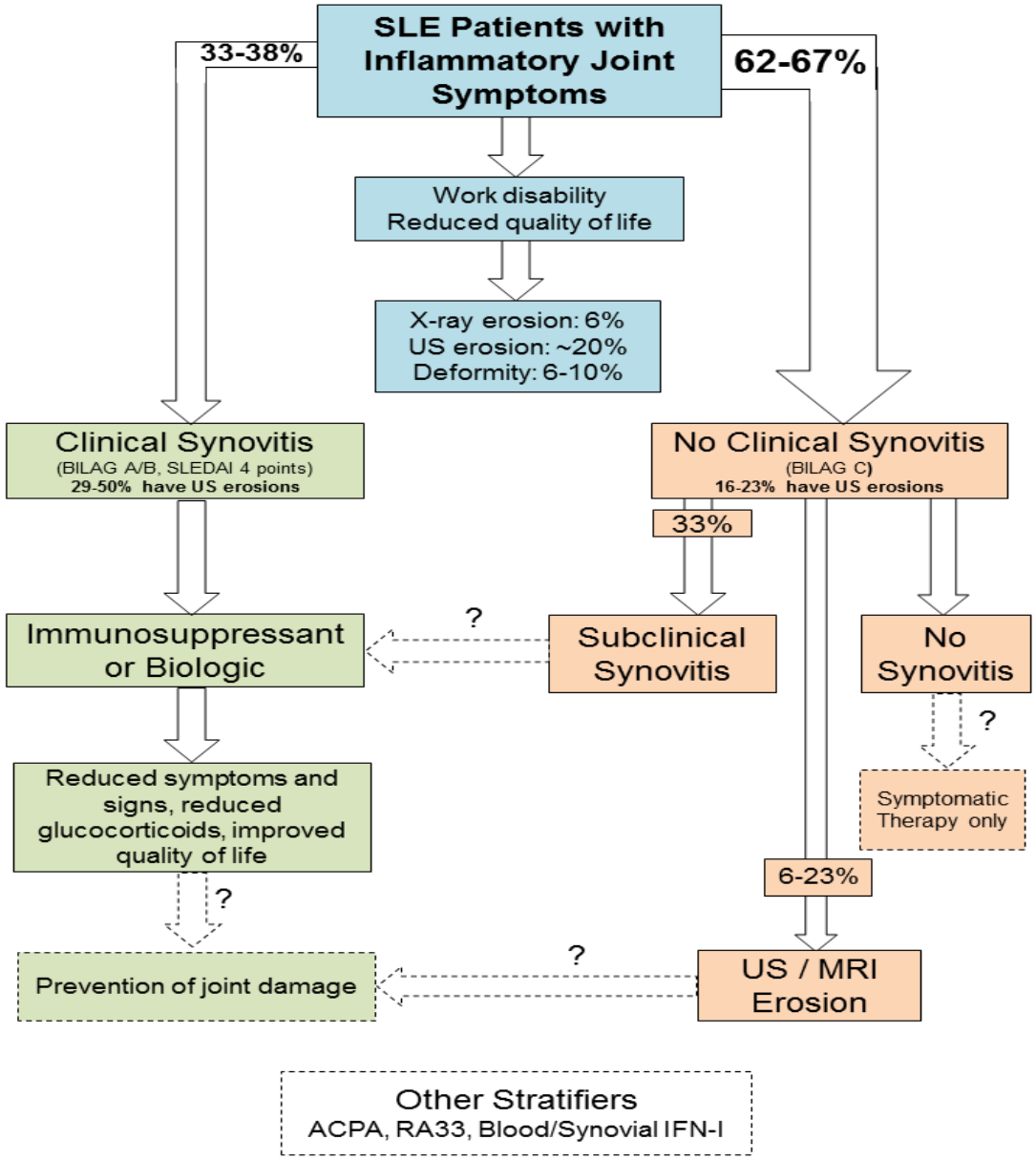
2.7 Treatment of musculoskeletal SLE

Although arthritis is a common feature in research populations, many clinical trials have neglected to report response in individual organ domains. In clinical practice, conventional therapy for SLE, i.e. (azathioprine, MMF, or cyclophosphamide) is frequently selected

because of their established efficacy in the treatment of other organ domains. However, in RA and other inflammatory arthritis, these agents have been shown to be less effective for arthritis than methotrexate. For this reason, methotrexate is often selected in SLE as a first-line immunosuppressive as a reflection of RA data [2]. Evidence for the overall efficacy of methotrexate for the treatment of non-renal SLE is mixed. Steroid-sparing, but not global disease activity reduction (Systemic Lupus Activity measure and SLEDAI) was concluded to be the effect of methotrexate in SLE patients found in one randomized control trial[84]. However, two smaller randomized trials did demonstrate some efficacy in arthritis-specific outcome measures [152, 153]. Similarly, in trials of biologic therapies, a few have reported organ-specific outcomes including arthritis and differences in efficacy between individual domains, especially comparing skin and arthritis domains. Musculoskeletal domain is frequently one of the most responsive organ systems. Belimumab is the only biologic therapy licensed for SLE. Musculoskeletal domain was reported to be one of the most common manifestations at baseline in two phase III studies on belimumab [154, 155]. BILAG domain responses in arthritis following belimumab suggest it is one of the most responsive organ systems [156]. Pooled post hoc analysis showed 60.7% of the patients in the musculoskeletal domain with active disease at baseline improved by at least one BILAG grade, compared to 50% of those on placebo. The Musculoskeletal domain outcomes were somewhat better than the results in the mucocutaneous domain (the next most common manifestation) which had improvement rates of 47.8 and 39.1% for the combined active and placebo groups. No substantive difference was observed between groups for the less common manifestations of renal and haematological domains. Further, rates of worsening reduced in the musculoskeletal domain from 5.0 to 3.9/3.8% for the 1 and 10-mg/kg active groups in musculoskeletal disease. By comparison, rates of worsening in the mucocutaneous domain were 4.5, 4.3, and 5.4% in the placebo, 1 and 10-mg/kg arms. Similarly, improvements were seen in the quality of life domains of the Short Form Survey 36, such as physical function and bodily pain[157]. A study of abatacept in patients with lupus arthritis, discoid lupus and lupus pleuritis showed a reduction in BILAG-defined flare rate for arthritis with abatacept but not

discoid lesions [158]. Our own group's open-label data suggests a similar pattern of efficacy with rituximab in SLE, with consistent efficacy in musculoskeletal disease but variable efficacy in mucocutaneous manifestations, and non-response in discoid lupus [159, 160]. Although phase III trials for the B-cell-targeted biologic epratuzumab were negative, earlier phase II data reported efficacy for epratuzumab in the musculoskeletal BILAG domain [161]. Phase II data on type I IFN-targeted biologics, sifalimumab, and anifrolumab included joint counts as secondary endpoints, demonstrating greater reductions in treatment groups compared to placebo [46]. Overall, arthritis often appears to be more responsive to immunosuppressive therapy than mucocutaneous disease using existing validated outcome measures. Further, the literature suggests that arthritis has a greater breadth of responsivity to a wide range of conventional and targeted therapies.

Figure 2-2. Treatment of musculoskeletal SLE



ACPA: -citrulillinated protein antibodies. INF-I: Interferon-I, US: ultrasound, MRI: magnetic resonance imaging. BILAG index: British Isles Lupus Assessment Group .SLEDAI: Systemic Lupus Erythematosus Disease Activity Index. RA33: heterogeneous nuclear ribonucleoprotein A2/B1

Figure 2-2 summarises treatment of musculoskeletal manifestation of SLE. Current knowledge (solid arrows and boxes) and knowledge gaps (dotted arrows and boxes) in the treatment of inflammatory musculoskeletal SLE. The main gaps in the knowledge are: (i) the value of immunosuppressive treatment for subclinical synovitis is not proven, nor the outcome of symptomatic treatment only in patients with normal imaging; (ii) erosions are more widespread than radiographic studies indicated but their long-term significance and any benefit of immunosuppression, are unknown; (iii) although SLE is heterogeneous for serology and interferon status, these subgroups of SLE have not been investigated with respect to their response to therapy.

2.8 Clinical Outcome Measures for SLE

Measuring SLE disease activity in clinical research is very important for several reasons including patient outcomes and disease prognosis, differentiating between patient groups and differences between therapeutic responses. The British Society of Rheumatology (BSR) 2017 Guidance recommends that all patients should be monitored on a regular basis for disease manifestations, clinical activity, drug toxicity and co-morbidities [162]. Assessment of patients with SLE is notoriously challenging because of the complexity of the disease, its multisystem nature in the same patient, its fluctuating course and the absence of a gold standard tool that measures the activity of the disease[163].

There are several outcome measures used in SLE. Probably the most commonly used tools are the British Isles Lupus Assessment Group (BILAG), Systemic Lupus Activity Measure (SLAM), European Community Lupus Activity Measure (ECLAM), SLE Disease Activity Index (SLEDAI) and Systemic Lupus International Collaborating Clinics/ American College of Rheumatology (SLICC/ACR) [164]. While BILAG, SLAM, ECLAM and SLEDAI are disease activity indices, SLICC/ACR is a damage index. As SLE is a multisystem disease, all these outcome measures represent an assessment of all potential systems affected in order to produce a composite score. For this reason, the outcome measures are limited in their ability to provide a sensitive index of individual systems, such as the musculoskeletal system. The validated outcome measures such as BILAG and SLEDAI are based on the detection of clinical swelling and in cases of active arthritis without clear detectable swelling, may fail to capture true disease activity. Many other additional tools are used to measure the quality of life in SLE. Medical Outcomes Survey Short Form 36(F-36), for example, assesses the physical function, the social function, mental health impact, role impact from physical problems, role impact from emotional problems, energy level, pain levels and general health perception [121, 165]. Other functional measures include the Health Assessment Questionnaire (HAQ)[166], General Health Questionnaire [167], and Quality of Life Questionnaire [168] which have the applicability for use in other rheumatic diseases

aside from SLE.

2.8.1 *British Isles Lupus Assessment Group (BILAG)*

The BILAG score was developed in 1988 and modified in 2000. It is used to evaluate SLE disease activity in individual organ systems and was developed based on the physician's intention to treat. The revised BILAG Index (version 2004) measures disease activity (scored from grade A to E) in 9 body or organ systems affected by SLE based on clinical assessments and laboratory results [11, 169]. The BILAG-2004 index covers 97 items as opposed to 86 items in the classic BILAG and records disease activity occurring over the past four weeks. The BILAG items are scored as 0 = not present, 1 = improving, 2 = same, 3 = worse, or 4 = new based on the trajectory of activity in the proceeding four weeks, so not just present or absent. The numerical global BILAG-2004 score has also been introduced to facilitate comparison with other disease activity indices[170]. Each grade is weighted as follows: grade A = 12 points, grade B = 8 points, grade C = 1 point and grades D/E = 0. The global BILAG-2004 score is then calculated by adding the total points from the nine BILAG grades.

The BILAG 2004 has been designed and validated with the focus on the physician's intention to treat in SLE and is a modern version of the Classic BILAG assessment tool [11]. Although there are many similarities, the Classic BILAG included tendon contractures and avascular necrosis. These items were removed in BILAG 2004 because they were felt to represent disease damage and not disease activity. Classic BILAG was a commonly used tool in earlier SLE studies of the past century. At each patient's visit, the BILAG (classical and 2004) instrument assesses (general, renal, haematological, neuropsychiatric, respiratory, mucocutaneous and musculoskeletal systems). In this instrument, disease activity is graded on a 5-grade scale. Grade A represents a very active disease, for which a change in therapy is required. Grade B represents a moderately active disease and implies that the patient needs an increase in treatment. Grade C indicates mild stable disease and requires symptomatic therapy. Grade D represents no current disease activity. Grade E represents

no current or previous activity [171]. The validity of BILAG has been assessed in several studies. In 2010 Siavash Nasiri et al. studied the correlation between different laboratory investigations (ESR, C3, C4, anti-DNA) and SLE activity. The group also studied the construct and criterion validity of the BILAG index as a tool for assessing the activity of systemic lupus erythematosus. They demonstrated that the validity of the BILAG index as a measure of SLE disease activity, based on its construct validity. Construct validity was confirmed by the expected association between high BILAG score and high level of ESR and anti-dsDNA (OR = 2.6 (1.2 - 4.3) for ESR> 60 mm/h, OR = 2.5 (1.4 – 3.6) for anti-dsDNA greater than 5 times the normal value) and low level of C4 and C3 (OR = 4.8 (1.4 - 15.1) for C3 below half the normal limit, OR = 4.1 (2.3 - 5.8) for C4 below half the normal value) and high SLEDAI-2K score(OR = 215.6 (99.8 - 387.6) for a value of SLEDAI above 6). Criterion validity was confirmed by the increasing strength of the association between BILAG scores and raised disease activity[172]. Chee-Seng Yee and colleagues through a prospective multicenter longitudinal study assessed BILAG sensitivity. The group studied the relationship between changes in BILAG score and treatment alterations over two consecutive visits. The conclusion was that increases in BILAG scores was correlated with increasing treatment (coefficient multinomial logistic regression: 1.35; 95% CI: 1.01-1.70). This association was also found in the opposite direction [173]. The strong points of the BILAG include highlighting the importance of assessing patients' individual bodily systems rather than a global or overall score, it includes the important element of change in disease state with time, is sensitive to small changes [173] and seems to distinguish between disease activity and disease severity.

There are several problems however that linked with the BILAG. BILAG fails to capture minor improvement, is time-consuming, requires assessment by a trained person and it does not consider immunologic serology in its final score. Further, it omits some important clinical manifestations such as Raynaud phenomenon and antiphospholipid syndrome.

2.8.2 *SLE Disease Activity Index (SLEDAI)*

The SLEDAI was developed in 1985 as a clinical tool to classify SLE disease activity in the ten days preceding assessment. It is a scale of 24 clinical and laboratory parameters that assess nine organ systems. The score can range from 0 to 105 and is based on the absence or presence of various manifestations in the preceding 10 days. However, there are some weakness in SLEDAI score. SLEDAI does not score life-threatening manifestations such as pulmonary haemorrhage and haemolytic anaemia [174]. It was modified in 2002 to (SLEDAI-2K) the period of the assessment was extended from 10 days to 30 days. Another modified version of SLEDAI was developed for use in the Safety of Oestrogens in Lupus National Assessment (SELENA) study; SELENA-SLEDAI. A glossary was added and the modification allowed for documentation of persistently active disease in some descriptors, which previously were not scored unless they were new or recurrent such as rash, mucosal ulcers, and alopecia. Additionally, the SELENA-SLEDAI also accepts the presence of either the objective or subjective findings for the descriptor to be scored as present [175]. SLEDAI and its versions have the advantage of easy documentation and low administrative burden and that explains why it is one of the most commonly used tools in the clinical trials and longitudinal observational studies. However, there are some problems with it. It does not have the ability to detect the improvement or deterioration in the patient's symptoms, but instead only identifies the presence or absence of the symptom. For these reasons the SLEDAI responder index 50(SLEDAI-RI 50) was developed as a way of detecting improvement or deterioration. It records a ≥ 50% worsening or improvement in disease activity between visits[176]. The SLEDAI-RA 50 composite score cannot discriminate between different symptoms in the presence of the same disease activity score. In addition, the tool is less detailed in its capture of SLE disease severity and range of manifestations. For example, joint involvement is defined as having inflammation in two or more joints but cannot discriminate if the arthritis is mild or severe; also it does not include a myositis index. Finally, not all SLE-related manifestations are included in the SLEDAI-2K [176]. None of the versions has the ability in

capturing the partial response or progression of an existing feature because the score only reduced when the item is completely recovered.

2.8.3 *European Community Lupus Activity Measure (ECLAM)*

The European Consensus Lupus Activity Measure (ECLAM) was developed in 1992 to index disease manifestations in the last 30 days prior to patient assessment [176].

The ECLAM uses a list of disease activity items which a physician judges as present or absent. Each item has a different weighting and a maximum score of ten. For musculoskeletal disease, one point is awarded for either non-erosive arthritis or evolving arthralgia. ECLAM showed correlation greater than 0.72 with SLAM, BILAG and SLEDAI, and correlated with Physician global assessment(PGA) as the gold standard, both on a quantitative scale (0-10) and a qualitative scale (inactive to active) [177].

2.8.4 *Systemic Lupus Activity Measure (SLAM)*

The SLAM was released 1986 and revised two years later and renamed SLAM-R. The SLAM grades 31 items into 0-2 or 0-3 and provides a summated score. For musculoskeletal disease the scores are: 0 = absent; 1 = arthralgia only; 2 = objective synovitis; 3 = limits function. Bae et al. presented a study of 30 patients to evaluate the feasibility and construct validity of this new version. Reliability was estimated by analysis of variance, with 0.78 inter-observer reliability and 0.61 intra-observer reliability. Regarding construct validity, Pearson correlations were calculated for SLAM-R with PGA (0.87), levels of anti-dsDNA (0.51), C3 (-0.60) and C4 (-0.29) [178]. The SLAM is used to assess and capture disease activity in the last month. It includes 30 items that cover nine organs/systems and seven laboratory parameters. The score ranges from 0 to 84. The limitations are that the SLAM does not consider the severity of the disease. It also has many subjective items such as fatigue and joint pain that depend mainly on the report of the patient to rather than objective manifestations [11]. Similar to other activity indices, both the ECLAM and SLAM lack sensitivity in detecting change.

2.8.5 *SLE Responder Index (SRI)*

The SRI-4 is a composite tool that includes the BILAG, modification of the Safety of Estragon in Lupus Erythematosus National Assessment/SLE activity index (SELENA-SLEDAI) score and the 3-cm Physician Global Assessment (PGA). The SRI-4 has the ability to assess for improvement in disease activity in each organ alone and the overall condition [77]. A responder is defined as one who has (1) no new BILAG A or not more than one new BILAG B organ domain score ;(2) at least a 4 point reduction in SLENA-SLEDAI score and;(3) no deterioration from baseline in the physician global assessment by at least 0.3 points [22]. The SRI was derived following *post-hoc* analysis of a phase II belimumab study in SLE in order to identify subjects with a significant clinical improvement in disease activity and response to treatment [179]. They defined response as if fulfilling all of the following: (i) ≥ 4-point reduction in SELENA-SLEDAI score; (ii) no new BILAG A or two new BILAG B scores and (iii) no deterioration from baseline in the PGA by at least 0.3 points (or 10 % of 3-point VAS).

The advantages of SRI include: it minimises the limitations of each of the individual index that constitute this composite measure. However, the SRI has some significant differences in outcome from the scores from which it was derived. For instance, the BILAG component is only defined by no new worsening. Thus, a patient can qualify as a responder using SRI-4 when a feature of SLEDAI resolves, while other features (if present at baseline) remained the same or worsened to some extent (one BILAG B score). The applicability of this index for clinical practice is therefore currently less clear.

2.8.6 *British Isles Lupus Assessment Group-based Combined Lupus Assessment (BICLA):*

The BILAG-Based Composite Lupus Assessment (BICLA) is a composite index that was developed by expert's consensus of disease activity indices. BICLA was first used as the primary endpoint in the phase II randomised controlled trial (RCT) of epratuzumab in patients with autoantibody positive SLE [180]. Requirements for response were: (i) BILAG-2004 improvement (all A scores improved to B/C or D and all B scores improved to C or D);

(ii) no worsening in disease activity (no new BILAG A or no more than one new BILAG B score); (iii) no worsening of entire SLEDAI-2K score from baseline; (iv) no significant deterioration (<10% worsening relative to baseline) in physician's global assessment and (v) no treatment failure(defined as new or increased use of oral corticosteroids or other immunosuppressant above baseline).

The strong point of the BICLA index is that it requires a stringent response in all body systems that are involved at baseline and requires that there are no new flares in the other body systems. In addition, BICLA includes treatment failure which is clinically meaningful particularly in terms of disease burden and comorbidity perspectives, whether this may be termination of therapy, increment in daily oral prednisolone dose or adding of alternative immunosuppressant.

BICLA is disadvantaged by the administrative burden that requires formal training and it also requires further validation in clinical practice and clinical trials.

2.8.7 *Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) and the revised version (RCLASI)*

Skin involvement is one of the most common features of SLE. It is measured by an organ-specific tool (CLASI). CLASI is a comprehensive tool that comprises assessment for disease activity and damage in cutaneous lupus erythematosus (CLE). It aims to measure the level of active inflammation in the skin, scalp, and oral mucosa. For instance, lesions with greater visual intensity (dark purple is worse than faint erythema) and scaling are considered to be more active and would be scored appropriately higher than those without. The damage is defined as depigmentation, scarring or atrophy and scarring alopecia. It is reported that CLASI is valid, reliable and sensitive to changes [181, 182]. A four-point or 20% decrease in CLASI activity score has been shown to be the most specific criterion in classifying patients as responders or non-responders and also represents the minimal clinically important changes [183]. D Bein et al. reported that CLASI as an overall useful instrument to analyse disease activity and damage in Cutaneous Lupus Erythematosus. Nevertheless, the CLASI does not

reflect an accurate assessment of all disease subtypes; therefore, a revision of the CLASI (RCLASI) was derived by adding oedema or infiltration and subcutaneous nodules or plaques as descriptors for disease activity[184]. RCLASI has been used in clinical trials; however the limitations include high administrative burden and lack of use in clinical practice.

2.8.8 *Damage Indices*

As a direct result of the improvement in SLE therapies, the survival rate of individuals with SLE has increased. The downside is that the cumulative effect of chronic disease due to end-organ damage and cardiovascular or infectious complications. Different from the previously mentioned outcome measure, The Systemic Lupus International Collaborative Clinics damage index (SLICC) is used to record irreversible damage that may happen in SLE patients either due to disease, medications or any undercurrent illness that presents for at least six months, any other illnesses that has developed after the diagnosis of SLE [185]. The musculoskeletal damage items are muscle atrophy or weakness, deformity or erosive arthritis, osteoporosis with fracture or vertebral collapse, avascular necrosis and osteomyelitis. Although this tool is not useful in assessing the response to therapy, it can be used to evaluate the general health and SLE control over time.

2.8.9 *Blood investigations*

There are multiple autoantibodies that can be detected in SLE patients. Of these the most commonly detected is anti-double strand DNA(ds DNA) [186]. Rising anti-double strand DNA is sometimes associated with flare but cannot be used as a marker of a flare because the pattern is inconsistent for all patients with SLE and this is thought to be due to the deposition of the antibodies in the tissues at the peak of the disease [12, 187]. Anti-C1q antibodies are present in 20%–44% of SLE patients. Anti C1q antibody titres correlate strongly with global SLE disease activity scores, and so are predictive of the development of renal involvement or flares in SLE patients [12]. Anti-chromatin antibodies can be detected in around 69% of patients with SLE, and mainly in patients with lupus nephritis, but can also be found in patients with Sjögren's syndrome, and systemic sclerosis [22]. Anti-Sm and anti-Ro antibodies can be

found in patients with SLE. However, these antibodies are neither specific nor sensitive in the function of monitoring for disease activity.

Traditionally, both C3 and C4 levels have been used as one of the most reliable biomarkers of SLE disease activity. Individual patients however show variation in complement levels, and other weaknesses of complement as a biomarker is that they are acute phase response items, they may be low due to genetic deficiency, and can be found in low levels in non-SLE conditions [174]. A decrease in complement (C1q, C3 or C4) level is associated with an increased risk of renal and haematological activity in SLE [176]. The measurement of complement breakdown products (i.e. C3d or C4d) may also be useful as these tend to increase following SLE flare but can indicate impending disease activity [188]. They have the same limitations as C3, C4 and C1q levels.

2.9 Quality of life

As a result of its variable course, complications, and the side effects of the medications, SLE is a debilitating disease with a negative impact on quality of life. In particular, patients have a higher mortality rate, decreased productivity at work, and many psychological issues. Patients with SLE have a large disease burden. There are many quality of life domains of importance to SLE patients such as social and family life, pain, fatigue, work, and independence [189, 190]. In comparison with other chronic diseases and healthy controls, SLE patients have the lower health related quality of life [191].

SLE has a comparable effects on patients to that of AIDS, RA, and Sjogren's syndrome[192, 193]. However, the physical function and pain domains were more affected in RA patients than patients with SLE, which could be explained by the nature of RA as it affects joints predominantly. Objective assessments of disease activity and damage are judged only by doctors and do not consider the patient's perspective of their health [194]. Therefore, assessment of health-related quality of life (HRQoL) in conjunction with clinical measures of disease activity and damage indices provides a more comprehensive impression of the patient and their condition.

2.9.1 *Health-related quality of life*

Health related quality of life (HRQoL) refers to various aspects of life that are affected by health such as functional status but excludes income, job security and living conditions which are the other determinants of QoL [195]. Various measures have been described for health related quality of life, which are not specific to SLE, but have been reported in SLE trials. These are summarised in Table 2-3.

Table 2-3: Measures of quality of life used in SLE

Measure	Contents
Medical Health Assessment Questionnaire	1-Degree of difficulty 2-Satisfuction with function 3-Need for help in daily activities
Quality of Life scale	Material goods, health, interpersonal relationship, self, recreational activities and independence.
Arthritis Impact Measurement scale-2(AIMS-2)	Mobility , physical activity , dexterity, household activity, social activities, daily living activities, pain, depression , anxiety, arm function, social support, work
Medical Outcomes Survey Short Form(20)	Physical functioning, role functioning, social functioning, mental health, health perception, pain[196]
Medical Outcomes Survey Short Form(36)	Physical functioning, role limitations resulted from physical problems, bodily pain, general heath, social functioning, mental health, role limitations resulted from emotional problems, vitality[197]
EQ-5D	Mobility, self-care, usual daily activities, pain, and depression
Sickness Impact Profile(SIP)	Sleep and rest, eating, work; home management, recreation, mobility, body care and mobility; body and, social interaction, alertness, emotional behaviour, communication.
WHOQoL-Bref	Physiological, psychological health, social relationships and environment[198].

2.9.2 *Short Form-36(SF36)*

Short Form-36 is a reliable and widely used instrument to assess self-perceived health status [199]. This generic measure can be used in many conditions including SLE. It has been recommended by The Systemic Lupus International Collaborating Clinics group (SLICC). It has the ability to identify the mental and physical effects of SLE on the patients in the previous month [200]. It assess the limitations in physical activities, pain, social activities, mental health, vitality, and general heath perceptions [12]. SF-36 consists of 36 items and 8 domains including physical function, role physical, bodily pain, vitality, role emotional, mental health, social function, and general health. Scores for each domain are added up, and these scores are converted into eight 0–100 scales. Higher score suggests better health status. Eight domains can be combined into the physical component score (PCS) and mental component score (MCS) to give a better general overview of health. SF-36 has been used in several SLE studies and they reported that physical health section scores were somewhat lower than those of mental health, which may indicate that physical health is more likely to be affected in SLE patients [190]. However, this instrument is less sensitive to changes. It has a shorter version which is called SF-20. SF-20 comprises 20 items, which are divided into 6 domains relating to physical functioning, role functioning, social functioning, mental health, health perception and bodily pain. The results are assessed in 1−10 scale and then multiplied by 100 [196].

2.9.3 *EQ-5D questionnaire*

EQ-5D questionnaire was developed by an international research group, the EuroQol Group. Established in 1987, it comprises of 5 questions on mobility, self-care, usual activities, pain, and depression. EQ-5D is one of the most widely used generic health status measurement, and it has good validity and reliability. The questionnaire has the advantage of being quick to complete [201].

2.9.4 *WHOQOL*

There are two versions of WHOQoL. The full version has 100 questions and the shorter version (BREF) which is used more frequently in practice. WHOQOL-BREF measures the following quality of life domains: physical health, psychological health, social relationships, and environment [202]. Higher score indicates better quality of life.

Several studies examined the relationship between SLE activity tools and these measures of quality of life. Most of the studies reported either a negative or a weak correlation between these tools and HRQoL.

Study group	HRQoL instruments	Activity index	Was there correlation
Gladman[203]	SF20, HAQ,FSS,DDM,CED-D	SLEDAI	No
Hanly[204]	SF20	SLEDAI	Week
Gladman[205]	SF20	SLEDAI	Week
Vu [206]	SF36	SLEDAI	Only physical component Yes
Stoll[207]	SF20	BILAG	Week
Thumboo[208]	SF20, SF36	BILAG	weak for SF20, strong for F36
Doria[209]	SF36	ECLAM	No
Saba[210]	SF36	SLAM	No
Dobkin[211]	SF36	SLICC/ACR-DI	Yes

2.9.5 *Lupus-specific measures of quality of life: LupusQoL*

This is a questionnaire to measure QoL in adult patients who are diagnosed with SLE, and it is derived from patient interviews. It has been developed and validated in the United Kingdom (UK) and adapted for North American SLE populations. It can be used in clinical practice and

research. There are 34 disease specific items and 8 domains and it gives us information related to SLE and its effect on the health status such as physical health, emotional health, body image, pain, planning, fatigue, intimate relationships, and burden to others in the last 4 weeks. The scores range from 0 (the worst quality of life) to 100 (the best one) [212-214]. Each item is assessed by a patient with the use of 4-point Likert scale (0–4, where 0 means “all the time” and 4 – “never”) [215] .

2.9.6 *Lupus-specific measures of quality of life: SLE Quality of Life questionnaire (L-QoL)*

This questionnaire assesses the overall effect of SLE and its treatment on the quality of life. It has 25 items on the scale. The quality of life indicator is obtained by adding up all the points (from 0 to 25). It includes assessment of self-care, emotional reactions, and fatigue in true / not true response format [212]. Higher score indicates worse quality of life.

2.9.7 *Lupus-specific measures of quality of life: Systemic lupus erythematosus specific quality of life instrument (SLEQoL)*

Derived from health professionals and then verified by patients, SLE QoL has been developed to assess the quality of life in people with SLE [189]. It consists of 40 items, including six domains: physical functioning, activities, symptoms, treatment, mood, and self-images. Scores range from 40-280, in which the higher values correspond to worse quality of life [212, 216].

2.10 Comparison of musculoskeletal parameters between clinical indices across rheumatic and musculoskeletal diseases

Arthritis is a term often used to describe any disorder that affects the joints. Symptoms and signs of arthritis include joint pain, joint swelling, redness, warmth, early morning stiffness, decreased range of motion and function of the affected joints [217, 218]. Onset can be sudden or gradual. Since arthritis symptoms may vary between patients and across autoimmune rheumatic diseases (RMDs), it is important to compare and contrast currently available indices to assess musculoskeletal SLE and other RMDs, for which arthritis is a common manifestation including rheumatoid arthritis (RA), psoriatic arthritis (PSA) and primary Sjogren's syndrome. These comparisons are detailed below and summarised in Table 2-4

Table 2-4.Comparison of musculoskeletal arthritis parameters between clinical indices for SLE, RA, PsA and Pss:

MSK Parameters	SLE		Rheumatoid Arthritis			Psoriatic Arthritis	Primary Sjogren's Syndrome
	BILAG-2004	SLEDAI-2K	DAS-28	SDAI	CDAI	PsARC	ESSDAI
SJC	Severe: ≥ 2 joints; Moderate: ≥ 1 joint	≥ 2 joints	Total SJC = 28	Total SJC = 28	Total SJC = 28	Total SJC = 66	1-5 joints: 4 points ≥6 joints: 6 points
TJC	Severe: ≥ 2 joints; Moderate: ≥ 1 joint	≥ 2 joints	Total SJC = 28	Total SJC = 28	Total SJC = 28	Total SJC = 66	1-5 joints: 4 points ≥6 joints: 6 points
EMS	Mild arthritis or arthralgia: (worse in the morning with EMS)	No	No	No	No	No	Arthralgia accompanied EMS>30 mins: 2 points
Patient VAS	No	No	100mm scale	100mm scale	100mm scale	0-5 Likert Scale	No
Physician VAS	No	No	100mm scale	100mm scale	100mm scale	0-5 Likert Scale	No
ESR/CRP	No	No	Yes	Yes	No	No	No

SJC: swelling joint count, TJC: tender joint count, EMS: early morning stiffness, ESR: erythrocyte sedimentation rate, CRP:C-reactive protein.

2.10.1 *Musculoskeletal components in disease activity indices for SLE*

2.10.1.1 Musculoskeletal -BILAG-2004

Based on the glossary provided in the BILAG-2004 index, severe arthritis i.e. Grade A score is defined as active synovitis ≥2 joints with marked loss of functional range of movements and significant impairment of activities of daily living, that has been present on several days (cumulatively) over the last four weeks. While moderate arthritis or tendonitis/tenosynovitis i.e. Grade B score constitutes active synovitis ≥1 or tenosynovitis joint (observed or through history) with some loss of functional range of movements, that has been present on several days over the last four weeks. Mild arthritis or arthralgia i.e. Grade C score is defined as inflammatory type of pain (worse in the morning with stiffness, usually improves with activity & not brought on by activity) over joints/muscle inflammatory arthritis, which does not fulfill the above criteria for moderate or severe arthritis [169].

2.10.1.2 Muskuloskeletal-SLEDAI-2K

The outcome for muskuloskeletal-SLEDAI-2K is binary i.e. present or absent. Four points are assigned for Arthritis domain if a patient exhibits ≥2 joints with pain and signs of inflammation (i.e. tenderness, swelling or effusion) [219].

2.11 Disease activity indices for RA

2.11.1 *Disease Activity Score in 28 joints (DAS-28)*

DAS-28 score has been widely used to assess disease in the joints of RA patients in both clinical trial and clinics. Indeed, based on 2016 EULAR recommendation pertaining to treat-to-target approach in the management of RA, DAS-28 score is recommended to be calculated at frequent intervals while therapies are being given, until a patient's score suggests disease remission, or to a particular ESR or CRP level [220].

Ritchie and colleagues initially developed the Ritchie Articular Index (RAI) or the extended 66/68 joint counts [221]. However, the problem with RAI was that this assessment could be time-consuming to perform. A twenty-eight joint count score was then developed [222],

which focused on metacarpo-phalangeal joints (MCPs), proximal interphalangeal joints (PIPs), wrists, elbows, shoulders and knees.

DAS-28 score is a composite index consisting of the number of swollen joint count (SJC) in 28 joints, tender joint count (TJC) in 28 joints, blood results i.e. erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) as available and the patient's global assessment of disease activity on a 100mm visual analogue scale (VAS). The formula [223] for score calculation depending whether either ESR or CRP is used are as below:

a)DAS28(ESR) = 0.56*√(TJC) + 0.28*√(SJC) + 0.70*Ln(ESR) + 0.014*VAS

b)DAS28(CRP) = 0.56*√(TJC) + 0.28*√(SJC) + 0.36*Ln(CRP+1) + 0.0014*VAS + 0.96

The DAS-28 score ranges between 0 and 10. A patient can be classified as remission, low disease activity, moderate or severe based DAS-28 score of <2.6, between 2.6 and less than 3.1, between 3.1 and 5.1 and >5.1 respectively.

In terms of response to therapy, the EULAR has established response criteria depending on changes in DAS-28 score. Criteria for either a good, moderate or non-responder are described in (Table 2-5) [224, 225].

Table 2-5: EULAR response criteria

<table>
<tr><td colspan="2" rowspan="2"></td><td colspan="3">Reduction from Baseline</td></tr>
<tr><td>>1.2</td><td>≤1.2 and ≥ 0.6</td><td>< 0.6</td></tr>
<tr><td rowspan="3">DAS28 at follow up</td><td>≤ 3.2</td><td>GOOD</td><td rowspan="3">MODERATE</td><td rowspan="3">NON</td></tr>
<tr><td>>3.2 and ≤ 5.1</td><td rowspan="2"></td></tr>
<tr><td>>5.1</td></tr>
</table>

DAS28 is measured at two time points, usually before and after treatment. Degree of change (reduction) and ultimate DAS28 achieved are used to determine EULAR response.

The advantages of DAS-28 score include its discriminatory ability to differentiate (mild, moderate and severe disease activity) and identifying disease remission[226]. Furthermore, there is a clear relationship between the mean DAS-28 score during a certain period and the amount of radiographic damage that the patient develops in that time-frame. However, there are some disadvantages of this instrument such as the exclusion of assessment of the feet in both the SJC and TJC components as well as some degree of inter-rater variability in assessing the DAS scores, as different raters may classify a joint as swollen or tender to different degrees.

There were a few studies comparing the use of DAS-28 score and disease activity index in SLE. For example, a study which was conducted in the Sapienza University of Rome and compared the discriminatory sensitivity to detect disease activity between DAS-28 and musculoskeletal-SLEDAI-2K. The study showed that up to 50% of the SLE patients without joint involvement as defined by SLEDAI-2K showed a moderate to high activity according to DAS-28 [188]. Thus, this highlighted a weakness of binary outcome as per SLEDAI-2K and that a composite index might be more useful in the assessment of arthritis.

2.11.2 *Simplified Disease Activity Index (SDAI)*

Simplified Disease Activity Index (SDAI) is a composite index established to improve convenience in assessing disease activity for RA particularly in the clinic. This index comprises SJC and TJC in 28 joints, physician and patient global assessment of disease activity using VAS and CRP [227]. The formula to calculate the CDAI score is as below:

SDAI = SJC + TJC + Patient VAS + Physician VAS + CRP

The interpretation for total SDAI score is as follows: (a) 0.0 – 3.3 (Remission);

(b) 3.4 – 11.0 (Low Activity); (c) 11.1 – 26.0 (Moderate Activity) and (d) 26.1 – 86.0 (High Activity).

This use of this index was validated in three x phrase III clinical trials of leflunomide in RA. The results showed a significant association between the SDAI and the DAS-28, as well as

the HAQ scores of patients with active RA [227].

2.11.3 *CDAI (Clinical Disease Activity Index)*

The CDAI consists of the same components of SDAI but does not include CRP level. This is particularly useful in the assessment of response to biological therapy that directly suppresses inflammatory markers such as interleukin-6 inhibitors; tocilizumab, sarilumab and sirukumab [228-230]. The formula to calculate CDAI is as below:

CDAI = SJC + TJC + Patient VAS + Physician VAS

The interpretation for total CDAI score is as follows: i) 0.0 – 2.8 (Remission);

ii) 2.9 – 10.0 (Low Activity); iii) 10.1 – 22.0 (Moderate Activity) and iv) 22.1 – 76.0 (High Activity).0.0 – 2.8 Remission

CDAI had been correlated and validated with US scores in subjects with RA [231].

2.11.4 *American College of Rheumatology response criteria:*

ACR(American College of Rheumatology) core set outcome measure is another commonly used tool to monitor RA response to therapies in clinical trial [232]. It includes 7- variables; Tender and Swollen Joint count, ESR,CRP, health professional and patient assessment of the global status of pain and physical function[232]. ACR response is described in percentages as ACR20, ACR 50 and ACR 70. ACR20, for example is, based on at least 20% improvement of both tender and swollen joint counts, in addition to 20% improvement in at least 3 out of 5 other measures. ACR 20 now is one of the most commonly used outcome measures in rheumatoid arthritis clinical trials [233]. If the improvement is 50% or 70% in the trial it is called ACR50 and ACR70 respectively.

2.12 Disease activity indices for psoriatic arthritis

2.12.1 *Psoriatic Arthritis Response Criteria (PsARC)*

Psoriatic Arthritis Response Criteria (PsARC) was first developed In the Veterans Administration study of sulfasalazine in PsA [234]. This composite index comprises SJC in

66 joints [distal interphalangeal joints (DIPs), PIPs and MCPs of the hands, wrists, elbows, shoulders, acromioclavicular, sternoclavicular, temporomandibular joints, knees, ankles, mid-tarsals, metatarsophalangeal joints (MTPs) and interphalangeal joints of the feet], TJC in 68 joints [as above joints but to add hips], physician and patient global assessment of disease activity in a 0-5-point Likert Scale; 0= very good, no symptoms, no limitations on normal activities and 5= Very poor, very severe symptoms which are intolerable, inability to carry out normal activities.

A patient is considered a responder if fulfilling: i) improvement in ≥ 2 of the four tests (One of which must be the SJC or TJC score and ii) no worsening in any of the four measures. Improvement is defined as a decrease of ≥ 30% in the SJC or TJC score and a decrease ≥1 in either of the VAS global assessments [235].

2.13 Disease activity indices for primary Sjogren's syndrome

2.13.1 *Musculoskeletal-ESSDAI*

The EULAR Sjögren's syndrome disease activity index (ESSDAI) was generated in 2009. This composite index consists of assessment in 12 domains i.e. cutaneous, respiratory, renal, articular, muscular, peripheral nervous system (PNS), central nervous system (CNS), hematological, glandular, constitutional, lymphadenopathy and biological. Each domain is graded into 3–4 levels of activity (no, low, moderate and high) [236].

For the musculoskeletal component of this index, only arthralgia of inflammatory origin should be scored based on positive responses to both the following questions: i) Have you got pain in your hands/wrists/ankles and/or feet in the past four weeks? And ii) Are you stiff in the morning for at least 30 minutes?" The SJC and TJC calculations are based on DAS-28 score. Details for Musculoskeletal-ESSDAI scoring are as follows: i) 0 point (no activity): Absence of currently active articular involvement; ii) two points (low): Arthralgia in hands, wrists, ankles and feet accompanied by morning stiffness (>30 min); iii) 4 points (moderate): 1–5 (of 28 total count) synovitis and iv) 6 points (high): ≥6 (of 28 total count) synovitis.

2.13.2 *Joint count*

The total joint count is one of the simplest ways to assess peripheral joint activity. There are 78 joints in total for assessment. However, this may be reduced to a joint count of 68 in accepted abbreviated versions. As it is not possible to clinically evaluate hip swelling, the 66/68 joint count is also accepted. In addition, it is difficult to distinguish the DIP joints of the toes and sometimes these joints are omitted in assessments. Tender and swollen joint counts have been used for a long time in clinical practice and trials as a method of assessing the activity of rheumatoid arthritis [221, 237, 238]. It is a component of both the DAS 28 and the ACR criteria as a central component of patient assessment [239, 240]. Some patients may have severe joint pain with few swollen joints, while other patients may have many swollen joints but with little pain. The presentations of both of these types of patient are eligible and to receive immunosuppressive or an anti-inflammatory treatment [241]. Squeezing joints is subjective and considered an indirect method in the detection of disease activity. Many studies have shown that joint counts are poorly reproducible on an inter-observer and intra-observer basis [242-244]. There is no standard method in the assessment of joint tenderness because it is challenging to standardize the location and strength of the pain pressure stimulus. The degree of pressure applied can be different between assessors [221]. Ritchie and colleges developed the Ritchie Articular Index or the extended 66/68 joint counts [221]. The problem with the Ritchie Articular Index is that it was found to be time-consuming as the number of joint involved was considerably large. Twenty-eight joint count then has been developed [222] which focuses on hands, wrists, elbows, shoulders and knees. This index however omits the foot joints. Smolen et al. compared the reliability of the 28 joint count with the 66/68 joint count. They found that the measures could be highly correlated and were easier to administer [245]. Clinical examination however is less sensitive in the detection of synovitis compared to ultrasound. Kane et al. studied 22 patients with RA using ultrasound of the knees and independent clinical examination. The group concluded that clinical examination was less sensitive in the detection of soft tissue abnormalities in the knee

compared to ultrasound [246].

2.13.3 *Early Morning Stiffness*

Early Morning Stiffness (EMS) is an important symptom in the evaluation of SLE disease activity evaluation. The majority of patients find difficulty reporting their duration of early morning stiffness with respect to a cut-off time. Leiden university hospital has shown that the sensitivity of measurement of early morning stiffness using the patient VAS is more reliable than measuring its duration [174]. However, it is not currently used in the composite measures of disease activity for RA, PsA and SLE.

2.14 Objective outcome measures for arthritis:

2.14.1 *Conventional radiography:*

Plain radiographs may have a limited role in the diagnosis and monitoring of SLE arthritis. Plain film can show soft tissue swelling, atrophy and effusion. In patients with Jaccoud's arthropathy, marked ulnar subluxation and deviation at the MCP joints can be seen [247]. Radiographic erosions on the radial side of the metacarpal heads with sclerotic margin changes called "Hook" erosions" have been described in SLE [248]. However, because of the rarity of the x-ray findings above, the applicability of this imaging modality in SLE arthritis assessment tools is limited.

2.14.2 *Ultrasound:*

Using clinical synovitis to assess joints disease in SLE could potentially lead to over or underestimating the disease activity due to the subjectivity of clinical judgment of joint swelling. High-resolution musculoskeletal ultrasound (US) has been validated as a potentially more objective assessment tool in inflammatory arthritis [121, 249, 250] and the ability to assess mild or subclinical disease activity by detecting subclinical synovitis and assessing any minimal changes in RA allowing the assessment of tendons, tendon sheaths and bone surfaces as well [251-253]. This, however, was not yet fully established in the case of SLE arthritis. There are limited studies on the use of ultrasound to detected pathology in SLE.

However, these studies detected synovitis in wrist and hand in 25-94% of the SLE patients without any symptoms [121, 254], which can potentially be very significant. However, there are many limitations in ultrasound use. It is an operator dependent modality where sonographers visually analysis real time images and might score the level of synovitis differently. Most previous studies have reported synovitis based on any level of synovial thickening including the very mild ones (EULAR/OMERACT Grey Scale (GS) grade 1) with or without Power Doppler (PD) [255-263]. This is known to be not specific and could be found in other non-inflammatory conditions such as osteoarthritis [264] and anecdotally in patients with hypermobility. A recent systematic literature review highlighted the variation and the under-reporting of ultrasound abnormalities in many studies. Using ultrasound in assessing SLE using a more robust methodology, grading and definition could however have a promising role in SLE assessment similar findings to RA if more validation work established similar to the case in inflammatory arthritis. Ultrasound is a key theme of this thesis and is discussed in detail below in 2.17.

2.14.3 *Magnetic Resonance Imaging*

Magnetic Resonance Imaging plays a vital role the in diagnosis and monitoring of RA. MRI is considered the imaging gold standard in the assessment of synovitis [265, 266]. Regarding validity, MRI has shown a high correlation with the histopathology of RA synovium [267]. However, MRI is not widely used as an investigation modality in SLE. This is despite evidence that MRI can identify bone erosion and tenosynovitis/tendonitis related to SLE arthritis [124]. Ostendorf et al. investigated SLE patients with varying degrees of JA (n = 14) and identified bony erosions in 71% of the study population [268]. Boutry et al. used MRI to compare patients (n = 14) with RA, SLE and systemic sclerosis and found that most of the SLE cases had evidence of non-radiographic synovitis or bone erosion at the wrists, and second and third MCP joints. Erosion was detected within the wrists on MRI in all SLE cases, and in 61% of MCP joints [269]. However, MRI is disadvantaged by its high cost, relative inaccessibility, and the prolonged examination period which can be in excess of an hour per patient scanned.

Many people cannot tolerate an MRI study due to claustrophobia. It is therefore not an ideal tool for the routine clinical or research assessment of musculoskeletal disease in SLE.

2.15 Failure of Randomised Control Trials in SLE

There are more than 25 RCTs of biologic therapies in SLE and most of these studies have failed to reach their clinical end points [77]. There are several causes for this failure. Some of them relate to the nature of the disease while others relate to the outcome measures and study design. Firstly, SLE has a variety of manifestations which range from mild disease to life-threating features that are not easily captured or differentiated with precision in current assessment tools. As a consequence, most of the RCTs on SLE exclude patients with severe or uncommon manifestations of SLE. Secondly, the number of recruited patients is low in most therapeutic RCTs in SLE, and this can be attributed to the low prevalence rate of SLE, making it challenging to establish large cohorts [77]. Regarding the study design, the prescription of immunosuppression, especially corticosteroids and corticosteroid tapering, is frequently left to physician experience because of the lack of standardized protocols and on account of individual patient factors [77]. In addition, most of the RCTs recruit patients with more than one disease feature or system involved. The result would be more realistic if the study was designed to examine only one organ or system [77]. Finally, there is no shared definition of complete response or remission in the SLE trials, so study end points are often non-transferable and may not reflect true disease activity [77]. Hence, it can be concluded that RCTs in SLE fail to reach their clinical endpoints because of trial recruitment for a rare disease, the inadequate responsiveness of available outcome measures and the clinical endpoints focusing on achieving remission or complete response.

2.15.1 *EXPLORER Study: Exploratory Phase II/III SLE Evaluation of Rituximab*

The EXPLORER trial was a placebo-controlled, double-blind, multicentre study which recruited 257 SLE patients from North America population with moderate to severe non-renal and non-central nervous system lupus [270]. Patients with severe CNS involvement and severe renal disease were excluded due to safety concerns related to fitness to consent and

risk of placebo randomisation, respectively. Patients were randomised to receive either a cycle of rituximab, two infusions of 1000mg given two weeks apart or a placebo with continuation of the background immunosuppressant. All patients also received 0.5–1.0 mg/kg of steroids which were tapered to 10mg daily by week 10. The primary endpoint was to achieve and maintain clinical response (major, partial or no clinical response) at week 52, assessed using BILAG criteria. No difference in both major clinical responses and partial clinical responses was observed between the placebo and rituximab groups with overall response rates of 28.4% and 29.6% respectively; p=0.973. *Post-hoc* analysis indicated the superiority of rituximab versus placebo in the African-American and Hispanic subgroups. The rates of BILAG A flares were also lower in the rituximab group [270].

2.15.2 *LUNAR trial: Lupus Nephritis Assessment with Rituximab*

The LUNAR trial was a randomised double-blinded, placebo-controlled phase III trial. The study recruited and randomised 144 patients in a 1:1 ratio to receive either rituximab or placebo (n=72 each). Patients had active proliferative lupus nephritis (class III or IV). Patients administered mycophenolate mofetil and IV pulse steroid in the first three days of the study entry and afterward switched to oral steroid to be tapered within 16 weeks. This study also failed to show the superiority of Rituximab added to MMF in addition to steroid over MMF and steroid without Rituximab in achieving a complete or partial response at week 52. There was no significant statistical difference in the overall renal response (complete and partial) between the rituximab and placebo groups; 57% versus 46% respectively (p=0.180). The problems with this trial were the small sample size, the background of the high dose of steroids and immunosuppressant that could mask the effect of the rituximab on this group of patient. These people had a good response to the standard therapy, so the rituximab was not more effective than these medications [77, 271].

2.16 Lessons from these trials

Although both trials failed to meet their primary endpoints, there are several lessons to be learned mainly the issues regarding study design. The first issue relates to the aggressive background of immunosuppressant in addition to mandated concurrent high dose of oral prednisolone. As a result, more than half of the patients in both rituximab and control groups had become steroid-dependent, whereas in the LUNAR study, patients were also co-prescribed a high dose of MMF up to 3g/day. Thus, the intensity of these "standard of care" therapy might have masked the therapeutic benefit of rituximab against placebo. Secondly, the problem with outcome measures. It is thought that in EXPLORER data BILAG might have been scored inappropriately both as inclusion and as response criterion. The BILAG originally was developed as representing the physician's intention to change therapy. Despite a relatively poor clinical response and persistently high disease activity, withdrawals due to inefficacy were relatively low, with approximately 70% of patients remaining in the trial for one year as per trial protocol. Only one-third of patients achieved major clinical response (MCR) or partial clinical response (PCR), and post treatment mean global BILAG was approximately 8 (on the scale A=9, B=3, C=1). This suggests that either the treating physician's impression of the residual disease activity was actually less severe than the BILAG scores, or that the disease activity present at baseline was not as severe as the BILAG scores indicated, or both. Lastly, the primary endpoint used in EXPLORER required patients to meet a low disease activity 'landmark' (BILAG C or better in all domains) at six months, and then to not flare in the second 6 months. The first problem with this was the initial landmark was difficult to achieve since only 27% of patients achieved score C or better in all domains, thus considerably reducing the power of primary and secondary end points. The difficulty in achieving the 24-week landmark may have been (a) because most patients had considerably higher baseline scores than the one BILAG A or two BILAG B scores required in inclusion criteria, so even a considerable improvement in disease activity was not sufficient and (b) because BILAG B scores were sometimes poor at differentiating partial responses. For example, a mild transient

malar rash scored the same as deep scarring discoid while the number of joints with synovitis (scored as B) were highly variable. However, even in patients who did meet the 6-month endpoint, there was no evidence of a significant rise in BILAG total score again in the placebo arm since a high dose steroid regime might have been sufficient to restore stable disease when given with background immunosuppressant.

Both of the belimumab RCTs (BLISS52 and BLISS76) used a new composite index used as the primary endpoint; improvement in the SRI-4 at week 52 and both achieved their primary endpoints. There are several reasons for the success of these trials. First of all, BLISS trials recruited more than 1600 patients versus less than 400 patients recruited by rituximab trials, which may have magnified the side effect of the drug on top of standard of care. The second point is that in the belimumab trials patients were selected on the bases of stable moderate-to-high disease activity with serological activity so patients did not require induction therapy at baseline. Therefore these patients were not on an aggressive background regime of treatment and modifications to this regimen were restricted in order to avoid any significant benefit on disease activity. Finally, using the composite SRI as an outcome measure gives better responsiveness to these trials instead of using the sole BILAG index or sole renal response analyzed in rituximab trials.

2.17 Musculoskeletal Ultrasound

Ultrasound use for musculoskeletal system assessment was first reported by Dussik in 1958. Karl Dussik measured the acoustic attenuation of different structures including muscle, tendon and bone opening the door for its future musculoskeletal use. In 1972 a report was published about the use of ultrasound in musculoskeletal system to differentiate between Baker's cysts and thrombophlebitis [272]. In 1978 P.L.Cooperberg used ultrasound to show synovitis and to assess the result of rheumatoid arthritis treatment [273].

Power Doppler (PD technology has added great value for using ultrasound in assessing inflammatory joints diseases. Power Doppler can differentiate between active and inactive disease by showing tissue hyperaemia and neovascularization which could indicate active

inflammatory status [257, 259, 274]. There is a significant number of studies that validate the use of PD in assessing synovitis and tenosynovitis and found to have similar sensitivity and specificity of MRI in detecting synovitis [275-277]. Power Doppler is also responsive to change in disease activity and to therapy [278].

2.17.1 *Advantages of ultrasound*

There are many advantages for this tool such as using it for quantitative and qualitative real - time assessment. Ultrasound has been used extensively in the diagnosis, assess damage and medications response assessment in inflammatory arthritis. Many rheumatologists use ultrasound as a complementary tool to their physical joints examination [279, 280]. It is significantly cheaper modality that could be available in clinics for immediate real-time, non-invasive, radiation free assessment. Furthermore, it can be used for guided intra-articular injections which could enhance more accurate injectable medicines placement and facilitate aspiration in difficult procedures. Patients like having ultrasound assessment as it an opportunity for the patient to be educated about their disease and convinces them about treatment while the scan is performed face to face with the clinician [281-284].

2.17.2 *Limitations of ultrasound*

There are limitations for using ultrasound as it operator dependent needing sufficient long time of training which can be time-consuming. Ultrasound can also be affected by many artefacts and confounders and limited to transducers foot print and difficulties in achieving acoustic access to certain joints limiting the view to some joints [282]. As it is based on sound waves, it will get reflected by bones and limited by gas which means full 360 degrees visualisation of the area of interest would be limited.

2.17.3 *Ultrasound versus clinical examination*

Ultrasound has the ability to detect subclinical synovitis in patients without obvious clinical abnormalities and to differentiate between real inflammatory arthritis from conditions that mimic inflammatory arthritis such as fibromyalgia [282, 285]. Using ultrasound is more

sensitive than clinical examination in detecting synovitis [246, 286]. Ultrasound was compared with clinical assessment and it was found to be more accurate than clinical results in the determination of inflammatory activity and assessment of different joints [249, 287]. Ultrasound was observed to have the capacity to detect a greater number of joints with effusion and synovitis than clinical examination [246, 249].

2.17.4 *Ultrasound in other inflammatory arthritides*

In the study reported by Wakefield ,et al. ultrasound was a reliable modality in detecting erosion especially in early diagnosed RA more than conventional radiography and it was [288].

The diagnosis of rheumatic diseases in an early stage leads to early treatment and improves outcomes [282]. This might be difficult by just depending on the clinical examination and conventional radiography.

2.17.4.1 Ultrasound in Rheumatoid Arthritis

Ultrasound was found to be a valid tool is assessing different features of RA. It is well known that synovitis and tenosynovitis are the hallmark of RA activity and used for disease diagnosis and monitoring while erosions represent the damage due to RA and would have prognostic importance in terms of RA severity [282]. Ultrasound has been used extensively in the diagnosis and monitoring of RA; it has been proved that it is more sensitive than clinical examination and specific modality to assess joint structures [213, 248, 249]. Brown and colleagues studied 112 RA patients in remission and found 19% of the patients had subclinical synovitis despite being in clinical remission. The study reported an association between abnormal baseline ultrasound and the12 months progression of the disease [289]. In addition to the ability to detect subclinical synovitis, ultrasound can be very sensitive and comparable to MRI and better than conventional radiography in detecting bone erosions [288, 290].

2.17.4.2 Ultrasound in Psoriatic Arthritis

While clinicians think that the role of ultrasound in inflammatory arthritis is limited to detecting synovitis, tenosynovitis and erosions, it might have a role in detecting other pathologies and

diseases and might have different sonographic phenotypes that are not necessarily a copy of what we see in RA. The pattern of synovitis in Psoriatic arthritis (PsA) for example is heterogeneous and affect the surrounding tissues in terms of tissue oedema, tendinitis, osteoproliferation and joint peri-enthesitis and enthesitis [291]. Gisondi et al. studied patients with psoriasis with no history of musculoskeletal symptoms and ultrasound was able to detect entheseal abnormalities in a large number of them [292]. Naredo et al. studied 162 psoriatic patients and compared them with control group and they found synovitis in 3% and 1.3% respectively, enthesopathy was detected in 11.6% and 5.4% of psoriasis and a control group [293]. Zabotti et al. compared both early rheumatoid arthritis and early Psoriatic arthritis by using ultrasound and they found that patients with RA had more synovitis than psoriatic patients. While in psoriatic arthritis patients-soft tissue oedema was the most prominent findings [294]. Schoellnast et al. used MRI to compare RA and PsA patients; they stated bone erosions were more common in RA and periostitis were more frequent in PsA patients [295].

Given the example above about the role of ultrasound in RA and PSA, it is important to note that no one so far tried to describe a different sonographic phenotype in SLE to potentially explain different musculoskeletal symptoms in this disease.

2.17.5 *Ultrasound scoring system*

Multiple scoring systems have been used to assess synovitis and erosions (Table 2-6). The Outcome Measures in Rheumatology (OMERACT) group have provided standardised definitions of pathology visible on ultrasound, based on expert consensus [296] and their EULAR-OMERACT scoring system reliability was tested and most commonly used in clinical trials [297, 298]. In this thesis the ultrasound abnormalities was defined and scored according to OMERACT-EULAR definition: (a) Synovial effusion: abnormal intra-articular material which is compressible and usually anechoic/hypoechoic compared to subdermal fat (PD is absent), (b) Synovial hypertrophy: abnormal intra-articular material which is not compressible, is usually hypoechoic in comparison to subdermal fat and may be observed with/without PD, (c) Tenosynovitis: anechoic/hypoechoic thickened tissue, seen with/without fluid within the tendon

sheath and in two perpendicular planes (with/without PD),(d)Cortical erosion: an intra-articular discontinuity of the bone surface visible in two perpendicular planes [299]. Similar to synovitis, there are multiple erosion systems mostly binary while many other used 0-3 scales based on either the size or extent of the erosions (Table 2-6)

Table 2-6. Semi-quantitative methods of scoring pathology on ultrasound of different studies:

Parameter	Scoring method	Grading definition
GS effusion	**Szkudlarek et al.**	0: none, 1: minimal amount of joint effusion, 2: moderate amount of joint effusion (without distension of the joint capsule), 3: extensive amount of joint effusion (with distension of the joint capsule) [300-302].
	Leeds Score	0: none, 1: mild, flat thickening, 2: moderate thickening, 3: marked thickening [303, 304].
GS hypertrophy	**Szkudlarek et al.**	0: none, 1: minimal synovial thickening (filling the angle between the periarticular bones, without bulging over the line linking tops of the bones) 2: synovial thickening bulging over the line linking tops of the periarticular bones but without extension along the bone diaphysis, 3: synovial thickening bulging over the line linking tops of the periarticular bones, with extension to at least one of the bone diaphysis 4: extension to both diaphysis [300-302].
	EULAR/ OMERACT	0: no hypertrophy independently of presence of effusion, 1: minimal; hypertrophy with or without effusion up to level of horizontal line connecting bone surfaces, 2: moderate; hypertrophy with or without effusion extending beyond joint line but with upper surface convex (curved downwards) or hypertrophy extending beyond joint line but with upper surface flat, 3: severe; hypertrophy with or without effusion extending beyond joint line but with upper surface flat or convex [258, 264, 265].
PD synovitis	**EULAR/ OMERACT**	0: none, 1: minimal; three single PD spots or up to one confluent spot and two single spots or up to two confluent spots, 2: moderate; greater than grade 1 but 50% of the background GS [298, 305, 306].
	Newman et al.	0: no or minimal hyperaemia, 1: mild hyperaemia, 2: moderate hyperaemia, 3: marked hyperaemia [307].
Erosion	**Zayat et al.**	0: none, 1: erosions covering less than one third, 2: erosions covering between one- and two-thirds, 3: erosions covering more than two-thirds of the bone surface [308].

Parameter	Scoring method	Grading definition
	Szkudlarek et al.	0: regular bone surface. 1: irregularity of the bone surface without formation of a defect seen in 2 planes. 2: formation of a defect in the surface of the bone seen in 2 planes [300-302]. 3: bone defect creating extensive bone destruction
	Wakefield et al.	Small: diameter <2mm, Moderate: diameter 2–4 mm, Large: diameter >4 mm [309].
GS tenosynovitis	**EULAR/ OMERACT**	0: normal, 1: minimal, 2: moderate, 3: severe [298, 305, 306].
PD tenosynovitis	**EULAR/ OMERACT**	Visible in 2 perpendicular planes and excluding normal feeding vessels… 0: no signal 1: peritendinous focal signal within the widened synovial sheath (i.e. signals in only one area of the widened sheath) 2: peritendinous multifocal signal within the widened synovial sheath (i.e. signals in more than one area of the widened sheath) 3: peritendinous diffuse signal within the widened synovial sheath (i.e. signals filling most of the widened sheath). In the presence of abnormal intratendinous signal (visible in 2 perpendicular planes and excluding normal feeding vessels) in addition to grade 1 or 2 peritendinous PD signal, increase grade by one point [298, 305, 306].
GS hypertrophy and PD synovitis combined	**EULAR/ OMERACT**	0: normal; no hypertrophy or PD, 1: minimal; GS=grade 1 and PD≤ grade 1 2: moderate; GS=grade 2 and PD≤ grade 2 or GS=grade 1 and PD=grade 2, 3: severe; GS=grade 3 and PD≤ grade 3 or GS=grade 1 or 2 and PD=grade 3 [298, 305, 306].
Tendon damage	**EULAR/ OMERACT**	In longitudinal and transverse planes… 0: normal, 1: minimal, 2: moderate, 3: severe [298, 305, 306].

GS: gray scale, PD: power Doppler

2.17.6 *OMERACT Filter and Ultrasound*

Ultrasound enables evaluation of joints and peri-articular structures based on GS appearance and PD in multiple planes. It is widely used in clinical practice to assess patients with inflammatory arthritis, it is relatively affordable and less time-consuming than other imaging methods [310]. There has been a wealth of publications that have confirmed face, content, construct and criterion validity, reliability, responsiveness and feasibility [121, 254, 258, 262, 311-318]. Other aspects of the effectiveness of ultrasound as a tool in the assessment of early inflammatory arthritis (IA) are discussed below, according to the criteria outlined within the OMERACT filter [297]. Having ultrasound been scrutinised in terms of reliability and validity in RA, its application in SLE would probably need to follow similar steps but to a lesser extent to proof the concept and allow the use of ultrasound in SLE clinical assessment and clinical trials. In this thesis, face, content and construct validity are tested in chapter 5 and 6, criterion validity tested in chapter 9 and responsiveness validity in chapters 6 and 8.

Table 2-7: OMERACT Filter:

Category	Type	Description	Chapter of thesis
Truth	Face Validity	The theoretical plausibility of a measurement tool for its intended use.	Chapter 5:
	Content Validity	The completeness of a tool to reflect the entirety of the concept it intends to measure and the necessity for inclusion of all the components within the measurement tool (i.e., do all its aspects contribute uniquely to the overall measure).	Chapter 5:
	Construct Validity	Agreement with other measures which are theoretically related and lack of agreement with those which are not.	Chapter 5:
	Criterion Validity	Agreement with an ideal or 'gold' standard. This includes: Concurrent validity: agreement with a 'gold' standard assessment conducted simultaneously with the proposed new measurement tool. Predictive validity: agreement with a 'gold' standard assessment carried out in the future, i.e., the ability of a tool to predict a future state.	Chapter 9:
Discrimination	Includes the ability of a tool to differentiate between health and disease, as well as between disease severity states (including reliability and responsiveness).		
	Reliability	The ability of a tool to detect severity states with consistency. For example, between equipment or between observers (inter-observer) and by the same observer over time (intra-observer).	Chapter 7 and 8
	Responsiveness	The ability to detect differences in severity over time, e.g., for monitoring response to treatment.	Chapter 6:Chapter 8:
Feasibility	The practicality of using the measurement tool, including involved time and financial costs.		ROOTS

2.17.7 *Erosion*

Ultrasound is a reliable tool in detecting bone erosion and has more sensitivity than pain X-ray; this has been demonstrated by many studies. Ultrasound has been shown to be more sensitive than conventional radiography in detecting erosions [309] including very early stages of rheumatoid arthritis[319]. Zayat et al. investigated the specificity of ultrasound detected bone erosion in RA patients. They compared their ultrasound findings with other diseases including gout, OA, psoriatic arthritis and normal volunteers and reported the possibility of

describing certain features of erosions that can be related to RA than other as well as the higher specificity and sensitivity of ultrasound detected erosions in specific joints such as the 5th MTP in RA patients [308]. Backhaus et al. compared clinical assessment, conventional radiography, MRI, ultrasound and 3- phase bone scintigraphy in patients with different types of arthritis (RA, Spondeloarthropathy, and arthritis associated with connective tissue disease). They found that ultrasound was more sensitive than MRI in detection of synovitis and tenosynovitis and MRI was more sensitive than conventional radiography in identifying early destructive arthritis [320]. In the current practices and clinical trials, ultrasound detected erosions have become an integral of ultrasound reported abnormalities in inflammatory arthritis especially with advanced high resolution ultrasound technology that has been able to detect and measure erosions less the 1 mm in diameter. Although erosive abnormalities are traditionally less commonly reported in SLE, there might be some drift in this traditional belief with a better understanding of SLE using currently available imaging modalities.

2.18 Ultrasound and SLE

Ultrasound has a well-defined role in many rheumatic diseases like RA, but this role is not established yet in SLE [321]. The limited role of ultrasound in SLE might be due to lack of the full understanding of the pathogenesis of articular disease in SLE and the impression that joints inflammation is not common in connective tissue diseases (CTD) with the focus of other systemic illness such as cutaneous, renal and cerebral diseases dismissing the fact the joint pain can be responsible for a great deal of SLE patients symptoms. This might have led to less common use of ultrasound in assessing SLE and subsequently lack of standardised technique and variable reported ultrasound abnormalities [285]. As expected indeed from the previously demonstrated data on ultrasound with RA, many studies demonstrated the higher sensitivity of ultrasound over physical examination in detecting synovitis and tenosynovitis in SLE patient's [254, 312, 316, 322]. Knowing how limited and subjective clinical examination is and the impact of that on patient treatment, having a more sensitive and less subjective modality would mean better treatment selection and more accurate assessment avoiding over

treating patients with non-inflammatory joints pain or under treating patient with subclinical synovitis [323, 324]. However, before ultrasound can be used confidently in assessing SLE in practice and clinical trial, further validation work is still required. The growing and expanding interest of using ultrasound in assessing connective tissue disease including SLE has led to attracting the attention of few small studies which inconsistently looked at different aspects of SLE ultrasound detected joints pathology (Table 2-8).

Table 2-8. SLE ultrasound studies:

Study group	Synovitis	Tenosynovitis	Erosion	Joints assessed	Number of patients
Wright et al [311]	71-92%	65%	47%	Hands, Wrists	SLE=17
Iagnocco et al [312]	42%	44%	4%	Hands, Wrists	SLE=26, HC=15
Iagnocco et al [313]	87%	N/A	N/A	Hands, Wrists, Feet	SLE=62
Gabba et al [316]	42%	61%	26%	Hands, Wrists	SLE=108, HC=60
Torrente-segarra et al [259]	25%	7-39%	N/A	Hands, Wrists	SLE=58
Ossandon et al [258]	40%	N/A	0%	Knee	SLE=26,RA=25, HC=15
Dell Sedie et al [257]	80%	28%	12%	Hands, Wrists	SLE=50, HC=50
Mosca et al[325**]**	42%	38%	31%	Hands, Wrists	SLE102, HC=46
Dreyer et al [254]	81%	18%	6%	Hands, Wrists	SLE=33, HC=11
Yoon et al [318]	64%	4%	N/A	Hands, Wrists	SLE=48, HC=18
Bousi et al [262]	47-58%	N/A	4-18%	Hands, Wrists	SLE=62, RA=60
Ogura et al [326]	80%	93%	N/A	Hands, Wrists	SLE=15, RA=40
Lins et al [321]	48%	23%	5%	Hands, Wrists	SLE=64
Morales-Lozano et al [327]	3-27%	7%	1-12%	Feet	SLE=54, HC=60
Salliot et al [328]	40%	N/A	N/A	Hands, Wrists	SLE=151

N/A not assessed, HC: healthy control

Ultrasound in assessing SLE arthralgia

Most ultrasound studies demonstrated higher rate of arthralgia and lower rates of clinically detected synovitis in SLE if we compare it to other inflammatory arthritides. This is vital for clinical practice and trials because current clinical disease activity tools are all heavily weighted for the presence of synovitis. Assessors might find it difficult to work out how inflammatory is the ongoing arthralgia in SLE patients with the risk of over reporting or under reporting it as synovitis. However, in many of the above mentioned studies (Table 2-8) reported patients with arthralgia without clinical synovitis had abnormal ultrasound.

Iagnocco et al. demonstrated that SLE patients with arthralgia and swollen and tender joints on examination had more abnormal findings on ultrasound in comparison with patients without symptoms. They studied 62 patients with SLE; ultrasound findings (effusion, PD and /or synovial hypertrophy) were detected in a significantly high percentage of abnormalities (87% (54/62 patients). Twenty-nine patients of those had abnormal sonographic findings in the absence of clinical manifestations in their joints. They found that MTP[313] Similar results were described by Dreyer et al. as they studied 33 SLE patients and ultrasound and clinical examination were performed. They stated that ultrasound was able to detect wrist synovitis in 81% of the study patients with arthralgia in comparison to only 18% without symptoms at the time of the scan. Two-third of the patients had synovitis in the MCP joint in the patients with arthralgia but only 16% had MCP synovities in the symptomatic group [254]. Torrente-Segarra et al. recruited 58 SLE patients, 28 had arthralgia in the hand and 30 patients were asymptomatic as a control group. They showed that patients with hand arthralgia had more ultrasound abnormalities and high SLEDAI score with a higher level of anti dsDNA antibodies. 25% of patients had synovial hypertrophy, active joint synovitis was seen in 14% of the patients and tenosynovitis were detected in around 39%. Extensor degitorum and extensor carpi ulnaris were the most common tendon involved [221].

The issues with these studies are similar, such as the lack of validity, the absence of the gold-standard modality to check the reliability and the definition of synovitis which states grade 1

GS as significant and enough to classify it as synovitis. There is significant heterogeneity among these studies in clinical setting, patient's selection and methods. Most of the studies there was no information on the relationship between the usage of corticosteroids and or immunosuppressant and ultrasound findings because these medications have direct influences on cytokines and inflammatory cells which may interfere with ultrasound findings.

Can ultrasound detect subclinical synovitis in SLE?

Yoon et al. showed that subclinical synovitis was very common among SLE patients, ultrasound detected subclinical synovitis in around 58% of the patients and 4.2% had tenosynovitis. They stated that ultrasound could detect joint abnormalities before they become clinically obvious since they found that 39 % of the patients developed new musculoskeletal manifestations within six months after the ultrasound [318]. Ossandon et al. demonstrated that ultrasound was able to detect synovitis in 38% of patients who had normal clinical examination of the joint[329]. Mosca et al. found that 20/ 28 patients of their cohort with morning stiffness and arthralgia had at least one abnormality in their ultrasound findings (either joint synovitis or tendon involvement), only 22/56(39%) had clinical findings in the clinical examination [325].

In the largest scale study on ultrasound and SLE before this thesis, Gabba et al. used ultrasound in 108 consecutive Caucasian SLE patients; 69 were asymptomatic and 39 reported active manifestations at the time of recruitment. Generally, 64/108 patients had abnormal ultrasound; among them 42/108 ultrasound showed joint involvement while tendon involvement was seen in 44/108 patents. Synovitis was detected in 27 patients and bone erosions were revealed in 28 patients. The study found that symptomatic patients had abnormal ultrasound changes at joints, while those without symptoms (BILAG C and D) had more abnormalities in the tendon [316]. Despite the large sample size and clear design, this study has some limitations. The lack of standardisation in terms of the time of usage and doses of NSAID and corticosteroids before the ultrasound examination might have significant confounding effects on the ultrasound scores (GS and PD). Also, grade1 GS was considered

as synovitis in their ultrasound scores. Moreover, patients with rhupus were included in the study and most of the ultrasound abnormalities were detected in this subgroup and this might affect the result.

Ultrasound detected bone erosions in SLE

Erosions were reported in SLE patients in MRI studies. [330]. Several studies reported erosions in SLE patients. The ranges massively varied between 2-41% of SLE patients [8]. A limited number of SLE studies separated the non-rhupus and rhupus groups which could have led to the inclusion of CCP positive patient with known risk of developing erosions which could explain the big gap in the rate erosions reported by different studies [255, 260, 261]. Only Gabba et al. clearly defined the subgroup of Jaccoud's and they detected erosions in a significant rate of 17% of their cohort and they reported an expected high prevalence of erosions in the rhupus group around 88%. Among the 28/108 patients who had erosions; 26/28 had erosions in their hands and 5/28 patients only had erosions in the wrists[316]. This somehow disagrees with other previously mentioned studies reports of higher rates of abnormalities in feet.

Ultrasound detected Tendinopathy, Tenosynovitis and Entheseal disease in SLE

Tendons involvement is common in SLE patients with musculoskeletal involvement and may affect up to 65% of them[121]. The most commonly tendons involved are the extensor and flexor tendons of the wrists [255, 259, 260, 313, 314] with tendon rupture not uncommonly reported as well[255]. A.Delle Sedie et al. studied 50 patients with SLE by using the ultrasound; inflammatory signs were detected in the hands and wrists in 50% and 80% respectively. Tenosynovitis was detected in 28% [314]. Gabba et al found that PD signals in the tendons of 13/108 patients, flexor tenosynovitis was observed in 32/108 patients while 37/108 patients had extensor tenosynovitis and both were found in 22/108 patients[316].

A.Di-matteo et.al studied ultrasound detected entheseal involvement in SLE and reported that ultrasound was able to detect one or more abnormalities in at least one enthesis in around

68% (44/65) of their cohort which was mainly at the distal insertion of the patellar tendon[331]. Although a surprising finding, further validated larger scale studies using gold standards will still be required as entheseal disease is not necessarily thought to be common in SLE but with reported Achilles tendon rupture in SLE that would still be a possibility. Investigating the use of steroid or other potential causes are linked to such a surprising finding will need further consideration.

Ultrasound versus SLE clinical outcome measures in literature

A Limited number of studies assessed the relation between some of the clinical outcome measures and ultrasound abnormalities. Most studies failed to find a correlation between ultrasound synovitis and SLEDAI, except Gabba et al found joint synovitis was associated independently with high SLEDAI score(P=0.04; OR1.10;95% CI 1.01,1.21)[260] and Torrente-segarra et al. who also showed that patients with hand arthralgia had more abnormal findings in their ultrasound with high SLEDAI score [259]. There are many reasons that could explain the lack of correlation. In most of the studies, there were no details about the tools they used (where they used the global tool or just the musculoskeletal domain?). Small sample size would be probably the main reason for not having meaningful results as well. Interestingly, not many studies looked at the correlation of ultrasound with BILAG probably due to the complexity of BILAG tool, but those who looked, similarly found no correlation which could be explained by the same reasons mentioned for SLEDAI. The summary of the association between ultrasound and clinical outcome measures are detailed in (Table 2-9).

Table 2-9. Clinical outcome measures and ultrasound:

Study group	Clinical tool	Association with US
Wright [255]	SLAM, JAI, ACR/SLICC	No
Iagnocco [312]	SLEDAI	Yes
Iganocco [313]	SLEDAI-2K, ECLAM	No
Gabba [260]	BILAG,ACR/SLICC, SLEDAI	Yes
Torrente-segarra [259]	SLEDAI	Yes
Ossandon [329]	SLEDAI, TJC/SJC	No
Dell Sedie [257]	ECLAM	No
Yoon [318]	SLEDAI	No
Dreyer [254]	DAS28,SLEDAI,SLICC/DI	No
Ruano CA [332]	SLEDAI-2K, SLICC/DI	No
Morales-Lozano [327]	SLEDAI	No
Salliot [328]	SLEDAI	Yes

ACR: American College of Rheumatology, BILAG: British Isles Lupus Assessment Group, DAS: Disease Activity Score ECLAM: European Consensus Lupus Activity Measurement Index, SLEDAI: Systemic Lupus Erythematosus Disease Activity, SLICC: Systemic Lupus International Collaborating Clinics.

Predictive role of ultrasound in SLE

Several studies have shown the ability of ultrasound in predicting future structural damage as well as the development and appearance of musculoskeletal manifestations in asymptomatic patients [333, 334]. Piga and colleagues stated that the presence of a higher PD-synovitis score at baseline was predictive of musculoskeletal flare within two years since baseline ultrasound examination [333]. Corzo et al. reported that patients with abnormal ultrasound had a higher chance of disease progression and need to receive more medications such methotrexate than the patient who had normal baseline scan during six

years follow up period [335].

Ultrasound validity in assessing SLE

Pigga et al. recruited 26 SLE patients with different subtypes of SLE arthritis (Rhupus, Jaccoud's, Non-deforming non-erosive arthritis) to evaluate the presence of bone erosion by using CTultrasound. Ultrasound had accuracy 90%, sensitivity 36%, and specificity 98% compared with 93%, 57% and 93% in erosions detection in the dorsal and lateral aspects of second and fifth MCP, which were recognised as areas with the best ultrasound reliability. Also, ultrasound detected 90% of CT erosions in the wrist joints [336].

Ultrasound and laboratory markers in SLE

In most of the previously mentioned studies on ultrasound and SLE, there was no correlation between the ultrasound findings and laboratory investigations, clinical assessment and disease activity tools [257, 311, 312, 315]. There are a few numbers of studies that studied the relation between abnormal ultrasound and other demographics or laboratory variables. Yoon et al. found a relation between the high level of ESR and ant-dsDNA and ultrasound abnormalities [318]. Gabba et al. demonstrated that patients with low level of C3 and C4 had a higher chance of having abnormal musculoskeletal ultrasound findings [316]. Bell et al. observed an association between the ultrasound abnormalities and the high level of IL-6 [37]. This might emphasise the potential for under reported/ undiscovered correlation between some laboratory markers and ultrasound simply either due to studies size or design problem.

2.18.1 *Why patients have symptoms with normal ultrasound?*

Many patients with SLE have joint tenderness without any abnormalities in the ultrasound; this can be explained by tenderness over the joint is due to other unidentifiable reasons such as muscle, nerve or other surrounding structures might be the cause of the pain. Arthralgia is very common among SLE patients and it is not related to inflammation, it can be related to depression, fatigue or fibromyalgia and these are not related to disease activity [321].

2.18.2 *Deficiencies in the literature on Ultrasound in SLE* and *Issues with current studies on Ultrasound role in SLE*

There are many problems in the existing ultrasound studies in SLE patients. There is a wide range in the rate of ultrasound detected synovitis ranging between 10-82% of patients. This could be related to the method of reporting ultrasound due to the absence of consensus about the definition of ultrasound examination. In addition, most of the studies used semi-quantitative grading and the results most often presented as binary (Synovitis, No synovitis). The other issue is the heterogeneity in the patient selection as most of the studies did not separate rhupus group and the non-rhupus SLE group especially when they scored erosions. There was also heterogeneity in the joints selected for these studies where some scanned hands and wrists only, while others used feet or knees. Some of the studies included patients without musculoskeletal manifestations at the time of presentation and the control group varied between normal volunteers or RA patients. Most of the studies ignored the permitted dose and time of nonsteroidal anti-inflammatory and steroid before the ultrasound; these may interfere with the ultrasound scoring system and clinical signs. The other problem is the lack of uniformed definition of ultrasound synovitis and most of the available studies used GS1 with or without PD as a definition of synovitis and this is not specific because it can be present in normal people and patients with osteoarthritis. The absence of a gold standard to be used for a comparison domain like arthroscopy or histology. Lastly, the range of the frequencies of the ultrasound transducers varies from 5-18MHz that could have affected detection of tendons and joints abnormalities. Transducers with high frequencies (13-20 MHz) are usually used in musculoskeletal ultrasound because they have a high sensitivity in detecting minor morphological changes in the small joint [121, 337-339].

2.18.3 *MRI in Inflammatory Arthritides*

Magnetic resonance imaging (MRI) is commonly used as the gold standard imaging modality in assessing synovitis in both clinical and research settings in rheumatic diseases like RA. As a multiplane modality, it gives the clinician more information about joints inflammation and damage even in the early stage of the disease by exploring synovial membrane, tendons and bone. It has many advantages in comparison with conventional radiography like measuring response to treatment and higher sensitivity in detecting erosions and monitoring the bony damage over a short period of time. In addition, some recent data have shown that synovitis and bone marrow oedema detected by MRI have some prognostic implications in RA and it could be used in selecting patients for expensive trials that are targeting patients with severe disease [266]. MRI is highly sensitive in detecting the changes in the synovial membrane volume in response to therapies and follow the rate of progressive joint destruction [340].

MRI has many vital roles in musculoskeletal medicine. It is used to evaluate back pain and in the diagnosis of aseptic necrosis[341]. MRI is an excellent modality for visualizing the articular and periarticular structures in three dimensions giving a better definition of bony details in comparison to conventional radiography [342]. Recently, MRI has been used as a gold standard modality in assessing synovitis [4], it has the ability to detect changes in synovial membrane volume in response to therapeutic agents and monitoring the progression of joint destruction [343]. Images by MRI for the musculoskeletal structures have used T2 weighted images for the anatomical detail, to detect fluid or oedema and fat, which give high signals. Gadolinium is used as intravenous contrast to increase the sensitivity of detecting erosions and it is taken up at the sites of synovitis [344].

However, there are many disadvantages to this tool: It is time consuming since each examination takes a long time, expensive modality in comparison with other images, the use of contrast with risk of allergic reaction and renal side effects and it is not suitable for people with implanted magnetic metals and pacemakers. In claustrophobic patient, it can be

unpleasant and fearful experience as patients have to stay inside the tube for a long period of time (nearly 60 min) [345]. Extremity MRI (e MRI) created to address some of these problems. It is time and cost effective with less claustrophobia as patient needs to put the interested part to be scanned in the machine, but the problem it has less magnetic strength which affects image clarity and provides less field of view [346]and it is not available in each hospital [344].

2.18.4 *MRI and Erosion*

OMERACT has come with a consensus definition of MRI detected erosions which is according to the group is "A sharply marginated" bone lesion, with correct juxta articular localization and typical signal characteristics," which is visible in 2 planes with a cortical break seen in at least one plane" [330]. MRI has been described to have a higher sensitivity than CR for detecting erosion in many studies [342, 347]. Conventional Radiography is insensitive modality in detecting bone erosion due to many factors as the lucency of erosion in the CR Is attributed to the cortical bone loss, not to the trabecular bone loss which is invisible on CR as well as the presence of projectional superimposition that obscures erosion that enface to the beam of the x-ray[4]. Ostergaard et al. compared MRI and CR in patients with RA over five years in terms of detecting bone erosion. They found that MRI was able to detect new bone erosions at least one year earlier than the CR [348].

2.18.5 *MRI Synovitis:*

There are many MRI parameters that have been used as markers of synovitis; including the volume of the synovial membrane, synovial membrane thickness and signal intensity after contrast [4]. Currently, MRI is considered as the gold standard imaging modality in assessing synovitis due to the validation work done previously where there was sufficient correlation between MRI findings and histopathology [349, 350].

2.18.6 *Advantages of MRI compared to ultrasound:*

MRI has the advantage of visualizing deeper structures and larger area and it has the advantage of imaging soft tissues and fluid within the joint [342]. It can detect synovitis qualitatively and quantitatively, sensitive in detecting the therapeutic response in the early stage of the disease and the ability in evaluating the surrounding soft tissues like tendons, muscles, and ligaments that could be involved in the inflammatory process [351]. MRI is more sensitive in detecting erosions than ultrasound [351], and it has the advantage of detecting bone marrow oedema over the ultrasound [352].

2.18.7 *MRI in inflammatory arthritis other than SLE*

In early inflammatory arthritis (EIA), there is usually no abnormality detected using plain radiograph within 12 months of symptoms onset [353]. However, MRI has been shown to be more sensitive than conventional x-ray in detecting radiographic features of EIA [354, 355]. Furthermore, Krabben et al. used MRI to study EIA and compared this with the clinical examination. They reported that MRI detected 54-60% of joint inflammation which could not be detected clinically [356]. MRI may also be used as a prognostic biomarker where Van Steenbergen et al studied 102 patients with clinically suspected inflammatory arthritis. Patient's questionnaire, joint count and MRI were performed. MRI detected subclinical inflammation in 44% of patients with clinically suspected arthritis; of which 35% of them progressed to clinically detected arthritis within four months of follow up [357].

In patients with early RA, (onset within 2 years) Hoving et al. compared the use of MRI, ultrasound and plain radiography in the assessment of arthritis. They reported that MRI was the most sensitive tool for detecting bone erosions; twice as sensitive compared to ultrasound and conventional radiography [355]. This was also supported by Ostergaard et al. who reported MRI erosions could be detected one year earlier than conventional radiography. Notably, those with MRI erosions at baseline the relative risk of radiographic erosions at 5-year follow-up was 4.5 (95% confidence interval [95% CI] 2.6–7.6), compared with those without erosions at baseline [358]. Additionally, MRI was also the modality of choice for

detecting bone oedema as well as higher sensitivity in detecting synovial disease. However, ultrasound was more sensitive in detecting joint effusion and tendon sheath inflammation[351].

MRI also has the potential of differentiating different patterns in different diseases which improve our understanding of different diseases and help to differentiate between them radiologically. In psoriatic arthritis, for example, patients usually have more surrounding soft tissues involved and the distribution of the joints involved by arthritis could be asymmetrical, oligo or polyarthropathy [291]. Schoellnast et al. compared MRI findings of patients with Psoriatic Arthritis (PsA) and RA and they found that hand periostitis and synovitis were more common in the PIP joints in those with PsA while those with RA had synovitis and erosions more in the wrists [359]. A study was done by Narvaez et al. to evaluate the difference between the early stage of RA and PsA by using MRI. They found that the frequency of synovitis, bone erosions, tenosynovitis, subchondral bone oedema were the same in both groups. Nevertheless, the position of bone oedema was different between RA and PsA with this being near to cartilage and the subchondral bone in RA while for PsA, this was more at the diaphyseal and close to the enthesis. Indeed, they also found the entheseal involvement was more specific for PsA than RA[360].

Nieuwenhuis et al. performed MRI scan for 178 patients with early arthritis; tenosynovitis detected in around 65% of the total patients, which was most significant with patients with RA than the others. However, there was no association between positive ACPA and tenosynovitis [361]. It will be interesting to know if MRI could show different characteristics in other rheumatic diseases such as SLE.

2.18.8 *MRI sequences used in assessing synovitis and joints disease*

Being heavily investigated and used previously, MRI studies which planned to assess RA patients with inflammatory and destructive changes in the joints must include at least the following:

- T1-Weighted images before and after IV contrast injection in 2 planes.

- T2-wighted fat saturated sequence or STIR sequence if the former not available.

These two sequences added to contrast will allow identifying synovitis (I,e inflammation) with soft tissue oedema on STIR while the contrast will allow differentiating fluid from synovitis. Other features of inflammation such as bone marrow oedema or enthesitis could be visualised using the STIR sequence while the T1 and T2 weighted will allow good anatomical characterisation of disease as well as previous signs of inflammation such as fat atrophy.

2.18.9 *Definitions of joint pathologies in MRI scoring system*

***Synovitis*:** An area in the synovial compartment that shows above-normal signal intensity of thickness more than the width of the normal synovium which is judged by comparing T1-weighted images, obtained before and after intravenous gadolinium contrast.

MRI bone erosion: A sharply marginated bone lesion, with correct juxta articular localization and typical signal characteristics on T-1 weighted images with loss of normal low signal intensity of cortical bone and loss of normal high signal intensity of trabecular bone which is visible in 2 planes.

MRI bone marrow oedema: A lesion (which may occur alone or surrounding an erosion or other bone abnormalities) inside the trabecular bone, with unclear margins and signal characteristics consistent with increased water content.

***MRI joint space narrowing*:** Reduced joint space width in comparison to normal, as evaluated in a slice perpendicular to the joint surface.

MRI tenosynovitis: Peritendinous effusion (which is high signal intensity on T2 weighted fat-saturated or STIR images) and/or tenosynovial post contrast enhancement (signal intensity increases on T-1 weighted images before and after contrast injection), seen on axial sequences over ≥ three consecutive slices.

2.18.10 *MRI scoring systems*

Before the development of the scoring system, manual measurement of the enhancing synovium volume was used to evaluate treatment response and it was considered as a strong predictor for disease progression [362]. There are few MRI scoring systems with some more used than others. The Whole Body MRI (WBMRI) scoring has been used in some RA and Spondelo-arthritis (SpA) studies detect inflammation and structural damage in the axial joints, peripheral joints and entheses [363] while some podiatry focused trials used a regional score such as Forefoot bursa(FFB) used in RA and predict foot disability [364].

Gadolinium (Gd)-enhanced MRI is highly sensitive assessment for synovitis as the inflamed tissue with synovitis show increased signal intensity on T1-weighted image post-GD injection. On the other hand, contrast injection prolongs the time of examination, increases the invasiveness, increases costs and the general risk on patients with kidney involvement [365]. Omitting IV contrast has been used in some trials and it is reported that it does not have significant impacts on erosions and oedema scores but decrease the reliability of synovitis score [366].

2.18.10.1 RAMRIS scoring system

RAMRIS is a MRI scoring method validated and approved by OMERACT and widely used in clinical trial trials. It was established and validated from 1998-2002 by the OMERACT MRI Working Group and updated in 2016. It is a measure of the inflammatory manifestations of RA seen on MRI. RAMIRS comprises scores of bone marrow oedema, synovitis, tenosynovitis and erosions [330, 367, 368]. The score method used as the following:

Bone Erosion: Each bone (wrists: distal radius, distal ulna, carpal bones, metacarpal bases; MCP joints: metacarpal heads, phalangeal bases) is scored independently

The scale is 0–10, based on the percentage of eroded bone compared to the “assessed bone volume,” judged on all available images: 0 = no erosion; 1 = 1–10% of bone eroded; 2 = 11–20%, etc. Regarding long bones, the “assessed bone volume” is from the articular surface to

a depth of 1 cm, while in carpal bones it is the complete bone • In case a bone is fused with another bone, bone erosion is scored as 10 in the bone.

Bone Marrow Oedema/Osteitis*:* Each bone is scored separately (like erosions) marrow oedema

The scale is 0–3 based on the proportion of bone with osteitis, as: 0 = no osteitis; 1 = 1–33% of bone with osteitis; 2 = 34–66%; 3 = 67–100%.

Synovitis: Synovitis is assessed in 3 wrist areas (1. the distal radioulnar joint; 2. the radiocarpal joint; 3. the intercarpal and carpometacarpal joints) and in each MCP joint. The first carpometacarpal joint is not scored.

The scale is 0–3. Score 0 = normal, while 1– 3 (mild, moderate, severe) are by thirds of the supposed maximum volume of enhancing tissue in the synovial compartment.

Tenosynovitis**:** In the wrist, tenosynovitis is evaluated at six extensor compartments and 3 flexor compartments, between the radioulnar joint and the hook of hamate. At the level of the MCP joints, flexor tendons are assessed in an area from 1 cm proximal to 1 cm distal to each joint.

The score of tenosynovitis is based on the maximum width of the effusion and/or tenosynovial enhancement measured perpendicularly to the tendon.

The scale is 0–3, as for: 0 = no; 1 = < 1.5 mm; 2 = ≥ 1.5 mm but < 3 mm; 3 = ≥ 3 mm peritendinous effusion and/or post contrast tenosynovial enhancement.

The recommended images should include T-1 weighted sequences for erosions assessment, T-2 weighed FS or STIR to evaluate Bone marrow oedema. Tenosynovitis and synovitis evaluation by post contrast T1 in combination with non-contrast T-1 weighted images [367, 368].

2.19 MRI in SLE

There is limited data on using MRI in SLE assessment. The main focus of these studies was either of structural damage or potential complications of SLE such as bone abnormalities (avascular necrosis or tendon rupture). In these few studies however, MRI had the ability to demonstrate and identify the structural damage up to 94% of the patients and bone marrow oedema up to 14% [325].

Some MRI studies in SLE looked at erosions and Jaccoud's arthropathy (JA). The MRI pattern of arthritis in SLE patients was described before by Ostendorf and Sà Ribeiro in two uncontrolled series (14 and 20 patients, respectively) of patients with arthritis. Although the imaging protocol and definitions were different, they found a prevalence of bony erosions of 50-57 % with a significant advantage in sensitivity with respect to plain X-ray [369, 370]. The sample sizes were small in both studies and the focus mainly was on JA.

Few studies tried to look at synovitis however. Boutry et al. compared patients with RA, SLE, and systemic sclerosis. Synovitis was identified in all SLE patients mainly at the wrists, 2nd, and 3rd MCP joints. Despite not being visible on plain x-ray, erosion was seen in more than 60% of MCP joints and most of the wrist joints by using MRI [371]. Bell and colleagues investigated 34 SLE patients with arthralgia to see the extent of MRI-determined joint disease (erosion and synovitis) in SLE looking at phenotypes using MRI and RA antibodies. They found erosion in more than 90% of patients in the wrist and 61% in the MCP joints. Surprisingly in this small study, they found a fair bit of erosions in SLE patient even in the absence of ACPA which is revolutionary given the general concept of SLE as a non-erosive disease. All of the patients had wrist joints synovitis [269]. Ribeiro et al. recruited 20 SLE patients with JA. They had normal X-ray, but by MRI 10/20 had erosions. In addition to detecting tenosynovitis and synovitis in the majority of this group of patients [317]. Mosca and colleagues performed MRI for 93 SLE patients and compared the results with a healthy control group. They reported that MRI showed at least one erosion in (44/93) 47%of patients with SLE in their hand and (90/91) 99% of them at their wrists. In the healthy control group, the erosions were found in 9/46

(19.6%) and 45/46 (97.8%) at the hand and wrist, respectively. All of these findings of erosions in MRI studies might change the concept of SLE as a non-erosive disease, as it seems to be a disease of some erosive nature but the modality being previously used such as CR was not sensitive enough in detecting that.

With the unique ability of MRI in detecting bone marrow oedema, studies reported bone marrow oedema ranges 7.5-35.5% mainly at the hands and wrists of SLE patients [372]. Tani C et al., studied the MRI pattern of distribution of bone marrow oedema and joint erosion in hands and wrists of SLE and RA patients with healthy control. They reported that the prevalence of bone marrow oedema and erosion was similar in SLE and RA patients [365]. These figures which are higher than would expected from other studies but raise the question about the patient selection in this study and if SLE patients were ACPA and RF positive or a sub-selected group with known severe joints inflammation where selection bias might have affected the results.

Table 2-10.MRI studies in SLE

Study group	Joints examined	Erosion	Synovitis	Tenosynovitis	BME	Type of patients
Ostendorf [369]	Hands, wrists	57%	64%	71%	N/A	JA=14
Boutry[373]	MCP, wrists	61%	N/A	57-86%	N/A	SLE=14 RA=19 Sjogren=5
Sà Ribeiro [370]	Hands	50%	67%	95%	40%	JA=20
Mosca [372]	Hands, wrists	20-98%	N/A	N/A	7.5-35.5%	SLE=93 HC=46
Bell [374]	Hands, wrists	61-93%	53-100%	20%	7-13%	SLE=34 RA=15
Tani [375]	Hands, wrists	48-82%	N/A	N/A	4-30%	SLE=50 RA=22 HC=48
Zollars [376]	Hands, Wrists	90%	60%	85%	55%	SLE=20

N/A: not assessed, BME: bone marrow oedema, HC: healthy control

2.20 Knowledge Gaps for Imaging Synovitis in SLE

Although it is clear that patients with SLE without joint swelling may have imaging synovitis, there are several key areas of knowledge needed to translate this into changes in clinical practice. First, as highlighted in our systematic review, previous studies failed to report OMERACT grades of abnormality, failed to control for rhupus and failed to control for NSAID and glucocorticoid therapies. Second, most studies did not recruit consecutive series of patients in order to estimate the prevalence of clinical and imaging definitions of synovitis. Third, the clinical significance of ultrasound only synovitis has not been tested (i.e., whether it is associated with worse symptoms or serological measures of disease activity). These questions are addressed in Hypothesis 1, Objectives 1 and 2, Results chapters 5, 6 and 9.

2.21 Problems with responsiveness of current outcome measures

Systemic lupus erythematosus assessment instruments depend on the assessing physician judging whether each symptom is due to active SLE, damage due to previously inactive SLE, or another disease entity. This may be difficult, even in the hands of experts. Although the BILAG tool is very useful in the assessment of global disease activity, it was not designed to assess each system in an in-depth way. In the musculoskeletal domain, the domain score A is defined by severe synovitis while B is moderate synovitis, and C is arthralgia. However since the majority of patients never have clinical synovitis, so it has a limited ability to capture changes. For example, a change in the number of swollen joints from 28 to two would not change the BILAG score in the musculoskeletal system. It would remain as BILAG A despite the obvious clinical improvement. Conversely, a drop in the swollen joint count from two to one would change from BILAG A to BILAG B. BILAG C represents the presence of inflammatory joint symptoms, which again can vary between 28 tender joints and pain VAS of 100 to one tender joint and a VAS of 10. Similar to BILAG, the SLEDAI scores four points for arthritis in more than two joints and zero points for lesser degrees of arthritis. This outcome measure is therefore unable to capture partial change, and hence unresponsive. Examples of how these tools may misclassify disease response in SLE are shown in (Table 2-11).

Notably with other outcome measures in the ACR core set and the DAS28 this partial improvement would be captured better.

Table 2-11. Performance of difference outcome measures in a typical arthritis response:

Month	Tender	Swollen	BILAG-MSK	SLEDAI-MSK	Response vs. previous month		Comment	Prednisolone decision
					SRI-4	50% reduction		
0	20	10	**A** (severe and moderate arthritis rated same)	4	N/A	N/A	N/A	15mg daily
1	5	3	**B** (severe and moderate arthritis rated improving)	**4**	**No**	Yes	Clinically meaningful improvement but no SLEDAI / SRI response	Reduce to 10mg
2	5	2	**B** (moderate arthritis rated same)	0	Yes	**No**	Clinically trivial improvement but meets SRI criteria	Continue 10mg
3	5	1	**C** (moderate arthritis rated improving)	0	**No**	**Yes**	Clinically trivial improvement but meets 50% reduction criterion	Reduce to 7.5mg
4	5	1	**B** (moderate arthritis rated same)	0	No	No	Clinically unchanged but **increased BILAG** score as no longer improving	Continue 7.5mg

This illustrative example shows a typical patient with severe lupus arthritis assessed at four time points after starting a new therapy. At each time point a physician decision on modifying prednisolone dose is suggested. At each follow up time point, one of the clinical trial outcome measures (BILAG-MSK, SLEDAI-MSK, SRI-4 and 50% improvement) can be seen to be inconsistent with the joint count and likely physician's prednisolone decision regarding.

2.22 Effect of lack of reliable outcome measures on clinical trials in SLE

There has been a high failure rate of B cells targeted biological therapies in general in clinical trials. Negative trials include those of belimumab (which was later shown to be effective in other RCT [377-381] and rituximab (which nevertheless is in continued widespread use in clinical practice based on positive case series evidence). Hence, many commentators believe that clinical trials of these agents do not accurately capture their efficacy. Although these difficulties have to some extent been resolved by later trial designs, these have required very large cohorts of patients for such a rare disease, which makes the studies difficult to recruit and costly. Even in the later positive results of large phase III belimumab trials, effect size appeared small. Other, non-B cells-targeted therapies have also been proposed, but none of these has yet demonstrated efficacy.

2.23 Use of joint-specific outcome measures in SLE clinical trials

2.23.1 *Sifalimumab phase II trial*

Sifalimumab is a fully human monoclonal antibody (immunoglobulin G1 k), which targets interferon (IFN) signalling, a pathway that has been linked to the pathogenesis of SLE. Sifalimumab neutralizes the majority of IFN-a subtypes. It met its primary endpoint of SRI (4) in phase II randomized controlled trial comparing three doses with placebo, although was not progressed to phase III studies due to the superiority of another molecule, anifrolumab [114, 382]. In a post-hoc analysis of the data from the phase II study, patients who had at least eight tender and eight swollen joints at baseline were analysed for at least 50% improvement in joint counts. In (Table 2-12) I have summarized some of the key endpoints from that paper and also calculated the difference in response rates from placebo.

Table 2-12. Post hoc analysis of joint count improvement in the sifalimumab phase II trial:

	N	Placebo	200mg (%)	Δ vs. placebo	600mg (%)	Δ vs. placebo	1200mg (%)	Δ vs. placebo
SRI-4	431	45	58	**13**	57	**12**	60	**15**
BICLA	429	36	45	**9**	47	**11**	48	**12**
Swollen joints baseline	431	6.3	6.6	**N/A**	6.8	**N/A**	6.4	**N/A**
Tender joints baseline	431	10.1	10.4	**N/A**	8.6	**N/A**	9.3	**N/A**
50% Joints*	155	37	54	**17**	58	**21**	61	**24**

*50% improvement in joint counts, calculated only for patients who had at least 8 tender and swollen joints at baseline.

These would data would appear to suggest that the 50% improvement in joint counts was better able to differentiate treatment arms compared to the SRI-4 or BICLA. However, it must be noted that far fewer patients were included in the joint count endpoint as more musculoskeletal disease activity was required at baseline. Therefore, the musculoskeletal subgroup may also have responded differently to the SRI-4 and BICLA. This analysis was not presented in the paper and was, therefore, a question I sought to address in my research.

2.23.2 *Anifrolumab phase II trial*

The MUSE study was a multi-center, randomized, double-blind, placebo-controlled Phase IIb trial of anifrolumab, a monoclonal antibody that targets the shared interferon receptor, and therefore achieves better neutralization of interferon signalling than by targeting the various ligands for this receptor [382]. Patients with active SLE (defined as SLEDAI-2K ≥ 6 plus 1 BILAG-A boost or 2 BILAG-B relapses plus activity as seen by the physician VAS (0-3) ≥1) [47]. There was a randomization 1:1:1 to placebo, anifrolumab 300 mg or anifrolumab 1000

mg every 4 weeks. In addition, individual arms were subdivided according to the type I IFN signature. The primary endpoint was the SLE responder index (SRI, SLEDAI 2K reduction by ≥4 points, no new BILAG-A or no more than 1 new BILAG-B thrust, no worsening of ≥0.3 from the physician's perspective) combined with a reduction in the glucocorticoid dose from week 12 to week 24 to <10 mg / day, as a secondary endpoint with continuing glucocorticoid dose reduction at week 40-52 and a glucocorticoid dose of < 7.5 mg / day. Other outcomes were CLASI improvement of> 50% (if initially> 10) and> 50% reduction of swollen plus tender joints (if ever ≥8). A similar analysis to sifalimumab is presented below in Table 2-13.

Table 2-13. Post hoc analysis of joint count improvement in the anfirolumab phase II trial:

	n	Placebo	300mg (%)	Δ vs. placebo	1000mg (%)	Δ vs. placebo
SRI-4	305	18	34	**16**	29	**11**
BICLA	302	26	54	**22**	41	**15**
Swollen joints baseline	305	8.3	8.6	**N/A**	**8.3**	**N/A**
Tender joints baseline	305	10.5	12.2	**N/A**	11.6	**N/A**
50% Joints*	131	49	70	**21**	65	**16**

*50% improvement in joint counts, calculated only for patients who had at least 8 tender and swollen joints at baseline. SRI-4, systemic lupus erythematosus responder index using a 4-point reduction in SLEDAI; SLE, systemic lupus erythematosus; SLEDAI-2K, systemic lupus erythematosus disease activity index, BICLA: British Isles Lupus Assessment Group-based Combined Lupus Assessment.

In this case it is somewhat less clear whether the joint count criterion differentiated treatment groups better than the BICLA. However, comparing these data with those in (Table 2-12) highlights another important point. The baseline joint counts in the two studies differed, being higher in the anifrolumab trial. Even if a threshold of eight tender and swollen joints is required before analyzing for 50% improvement, there would still be a difference in the mean baseline joint counts of patients within that subgroup. Since the criteria for the different BILAG and SLEDAI grades are based on a fixed threshold of 0, 2 or 3 joints, the degree of mismatch between a 50% improvement and BILAG and SLEDAI response will differ depending on the

baseline joint counts.

Further post-hoc analysis of arthritis parameters was published separately [383]. In this publication, the emphasis was on comparing the improvements seen in patients with or without a high interferon signature at baseline. Surprisingly, almost all the patients in the trial had active arthritis (according to SLEDAI) at baseline. The authors reported three different measures of arthritis improvement: SLEDAI-2K improvement; BILAG-2004 improvement and mean change in joint counts. Interestingly, a different conclusion regarding the predictive value of the interferon signature was drawn depending on which of the arthritis measures was used (Table 2-14).

Table 2-14: post-hoc analysis for the anifrolumab trial:

	All patients		**IFN High**			**IFN Low**		
	Anifrolumab	**Placebo**	**Anifrolumab**	**Placebo**	**Δ vs. placebo**	**Anifrolumab**	**Placebo**	**Δ vs. placebo**
SLEDAI response (%)	56.7	42.4	56.2	39.7	16.5	58.3	50.0	8.3
BILAG improvement (%)	69.1	49.5	66.2	47.2	19	78.3	56.5	21.8
Change mean joint count	-5.5	-3.4	-4.9	-3.0	-1.9	Not given	Not given	-

SLEDAI: SLE Disease Activity index, BILAG: British Isles Lupus Assessment Group. IFN: interferon

2.23.3 *Combined post-hoc analysis of sifalimumab and anifrolumab trials*

Post-hoc analysis of the data from two 52-week studies of sifalimumab and anifrolumab. At Week 52, of the 736 patients recruited from both studies, 396 were SRI (4) responders, and 340 were non responders. They used different outcome measures to compare between the

responder and non-responder groups which included : The percentage of patients with a 7-point reduction in SLEDAI–2K; changes from baseline in clinical components of the SLEDAI–2K and PhGA scores; percentage of patients with BILAG ‘‘A’’ or ‘‘2B’’ flares; the numbers of SLEDAI–2K organ domains with improvement; and the percentages of patients with reductions in oral corticosteroid dosage to 7.5 mg/day, 50% improvement in swollen and tender joint count, and 50% improvement in the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI). A greater percentage of SRI (4) responders had a 7 point reduction in SLEDAI–2K score compared with non-responders ($p < 0.001$). SRI (4) responders had a greater mean percentage change from baseline in clinical SLEDAI and Physician GA score than non-responders ($p < 0.001$). Moreover, a lower percentage of SRI (4) responders had 1 flare as measured by BILAG ‘‘A’’ or ‘‘2B’’ flare rates, in comparison to non-responders ($p < 0.001$), whereas the mean number of organ domains with improvement in SLEDAI–2K was greater in SRI (4) responders vs. non responders ($p <0.0001$). Similarly, greater percentages of SRI(4) responders achieved a reductions in oral corticosteroid dose to 7.5 mg/day (for patients who were receiving 10 mg/day oral corticosteroid at baseline), as well as 50% improvements in swollen and tender joint count, and a 50% improvement in CLASI, compared with non-responders ($p < 0.001$).

2.24 Knowledge gaps for responsiveness in musculoskeletal SLE

As discussed above, although the BILAG and SLEDAI have been validated and shown to be responsive, their face validity and evidence from clinical trials suggest they may not be as responsive as arthritis-specific measures such as joint counts. These tools have never been formally compared. Further, their responsiveness has never been compared with an objective measure of synovitis such as musculoskeletal ultrasound. The relative value of BILAG and SLEDAI, clinical MSK evaluation (such as joint counts), and ultrasound defined synovitis has not been compared. Although ultrasound is not always convenient for routine practice and clinical trials, it may be possible to create a composite outcome measure for musculoskeletal SLE similar to the DAS28 and CLASI. Such a tool would ideally be validated against a gold

standard of inflammation, such as ultrasound, instead of against physician's evaluation or intention to treat as used for the DAS28 and CLASI. The information needed to define such a tool has been set out in the OMERACT filter [297].

These questions are addressed in Hypothesis 2 and 3, Objectives 3, 4, and 5 and Results Chapters 5, 6, 7 and 8.

2.24.1 *Treatment of subclinical synovitis in RA and impact on SLE*

The management of patients with RA has improved dramatically in recent years with the introduction of early intervention concept, the use of objective assessments as well as the availability of more effective biologic therapies. Disease remission is desirable and achievable. Based on current evidence and expert opinion to improve the management of RA, an international task force recently published recommendations in RA to achieve the optimal therapeutic outcomes. These guidelines endorse clinical remission as the primary goal for treatment of RA. Clinical remission is defined as the absence of signs and symptoms of significant inflammatory disease activity and includes an assessment of joints, acute phase response items and patient's and physician's global assessment. It is acknowledged that clinical remission may not be an appropriate and feasible target for all patient. Therefore, the main principle is to achieve an attainable target that reflects stable and as minimally as possible disease activity. This treatment to a (pre-defined) target encourages the use of a measure to assess the status of RA – most often using established composite index I.e. (DAS28, Simplified Disease Activity Index [SDAI], Clinical Disease Activity Index [CDAI]) [384]. Nevertheless, composite indices have their own limitations including underestimation of disease activity due to the insensitivity of clinical evaluation or the lack of acute phase laboratory markers. Other limitations include subjectivity of assessments components including tender joint counts and visual analogue scores. Moreover, the presence of joint damage may make the assessment of swollen joint counts difficult even in the hands of experts.

In order to overcome these problems, ultrasound imaging has the potential to monitor or to

target patients for remission. Cross-sectional studies in RA have demonstrated that ultrasound imaging influences clinical decision-making, modifying diagnosis +/- therapy decisions; whether these are associated with improvement in outcomes have yet to be determined [286]. Nevertheless, in patients who were in clinical remission, studies had shown joints demonstrating baseline PD had a 12-fold increased probability of developing erosions. It is therefore hypothesised that treatment according to an ultrasound target would lead to better long-term outcomes than treatment according to a clinical target [287-291].

The ARCTIC study (Aiming for Remission in rheumatoid arthritis: a randomised trial examining the benefit of ultrasound in a Clinical Tight Control regimen). Two-hundred and thirty eight patients were recruited. ARCTIC was designed to compare two tight control treatment schemes in patients with early RA and assessed whether incorporation of ultrasound information into treatment choices and targeting therapy towards imaging remission would lead to patient's improvement. The combined primary endpoints were sustained clinical remission, absence of swollen joints and inhibition of joint damage. The results displayed no difference in the primary endpoint and most of the secondary endpoints, which were based on symptoms and signs of arthritis between the group that targeted clinical remission alone versus those that targeted combined clinical and ultrasound defined remission [385]. There was a trend to lowering of erosion in the ultrasound arm though.

So, could ultrasound defined remission be used in SLE? It is important to note the differences between disease activity indices in RA and SLE. Current clinical disease activity indices in RA may be more sensitive to a change in therapy than musculoskeletal components in the BILAG-2004 or SLEDAI-2K in SLE. So, if we consider a patient with arthralgia, 20 tender joints, no clinical joint swelling, normal inflammatory markers, evidence of osteoarthritis or fibromyalgia and a patient VAS of 80/100, the RA and SLE instruments will perform differently. In RA, the DAS28 score will be 4.58, warranting increase in therapy. Thus, additional ultrasound information may have not impacted the overall outcomes since these patients would be over-treated anyway. However, in SLE, the investigators will deem these symptoms

to be unrelated to SLE, thus a score of BILAG D and SLEDAI 0 points for musculoskeletal involvement will be assigned instead.

Moreover, as described in previous section (2.18) the frequency of swollen joint is much lower in SLE than RA [386]. Therefore in symptomatic patients non-detectable synovitis, should ultrasound be introduced, subclinical synovitis may be detected more leading to an increase in therapy and better outcomes in the long run. Therefore, this provide rationale for ultrasound defined remission to be investigated in SLE.

2.25 Knowledge Gaps for treatment of Imaging Synovitis in SLE

Existing data suggest that there is a substantial amount of objective joint inflammation that is only detectable using imaging. Results chapters 5 and 6 will define this. However, in terms of treatment, it is not sufficient to just define which patients have imaging synovitis. Clinicians need to know whether these patients should be prescribed glucocorticoids immunosuppressant and biologics purely on the basis of the imaging findings. In order to test this, we need to know whether patients with imaging synovitis have a better clinical response to therapy than those no inflammatory findings on imaging. This is addressed in Chapter 7:

Additionally, we need to know which patients should be evaluated in clinical trials of new therapies. It is not clear whether current usual practice to include only patients with clinical synovitis (scoring on BILAG and SLEDAI) is appropriate. We need to determine whether clinical trials are feasible in patients with imaging-only synovitis, whether they can be conducted without the use of ultrasound endpoints and whether analysis of these patients can differentiate active and placebo treatment arms. In the cutaneous SLE in clinical trials, the CLASI detected more difference between treatment groups than the SRI-4, especially in the speed of onset of response. Novel tools for musculoskeletal SLE may achieve a similar result. It is also not known whether trials that focus purely on musculoskeletal SLE could use a more rigorous standard of care (e.g., lower doses of glucocorticoids) than were previously problematic in trials of multisystem SLE.

Chapter 3: Aims, Hypotheses, and Objectives

3.1 Aims-

The overall aims of this thesis are:

1. To improve the care of people with musculoskeletal symptoms in SLE by improving the accuracy of clinical assessment and identification of people who will benefit from treatment.
2. To improve the conduct of clinical trials in musculoskeletal SLE using novel outcome measures and trial designs.

Individual hypotheses and objectives for this work are summarised in Table 3-1 below.

3.2 Hypotheses

1. There is a substantial proportion of SLE patients with objective musculoskeletal inflammation that is symptomatic but not detected by existing clinical instruments
2. Existing validated disease activity instruments are poorly responsive for musculoskeletal manifestations
3. SLE patients with subclinical synovitis will clinically respond to therapy

3.3 Objectives

1. To evaluate a cross-sectional cohort of consecutive SLE patients with musculoskeletal symptoms for both clinical and ultrasound synovitis, and determine the clinical associations of subclinical synovitis
2. To validate ultrasound synovitis using MRI and describe MRI pathology in patients with SLE arthritis in detail
3. To perform a pilot study to explore the responsiveness of BILAG, SLEDAI, SRI4 with ultrasound and other clinical parameters in patients receiving treatment with glucocorticoids
4. To perform a definitive study to determine the responsiveness of each of these

parameters (the USEFUL study).

5. To determine whether patients with abnormal musculoskeletal ultrasound have better clinical response to glucocorticoid therapy compare to patients with normal musculoskeletal ultrasound (construct validity, USEFUL study).

Table 3-1: Summary of thesis structure

Knowledge Gap	Hypothesis	Objective	Results Chapter / Project
2.20: Knowledge Gaps for Imaging Synovitis in SLE	1.There is a substantial proportion of SLE patients with objective musculoskeletal inflammation that is symptomatic but not detected by existing clinical instruments	1.To evaluate a cross-sectional cohort of consecutive SLE patients with musculoskeletal symptoms for both clinical and ultrasound synovitis, and determine the clinical associations of subclinical synovitis	(5) Cross-Sectional Study: Defining Musculoskeletal Manifestations in Systemic Lupus Erythematosus.
		2.To validate ultrasound synovitis using MRI and describe MRI pathology in patients with SLE arthritis in detail	(9) MISTER
2.24: Knowledge gaps for responsiveness in musculoskeletal SLE	2.Existing validated disease activity instruments are poorly responsive for musculoskeletal manifestations	3.To perform a pilot study to explore the responsiveness of BILAG, SLEDAI, SRI4 with ultrasound and other clinical parameters in patients receiving treatment with glucocorticoids	(6) Pilot Longitudinal Study: Responsiveness of clinical and ultrasound outcome measures in musculoskeletal systemic lupus erythematosus:
		4.To perform a definitive study to determine the responsiveness of each of these parameters (the USEFUL study)	(8) USEFUL Study: Responsiveness of ultrasound and clinical variables
2.25: Knowledge gaps for treatment in musculoskeletal SLE	3.SLE patients with subclinical synovitis will clinically respond to therapy better than those with no objective evidence of inflammation	5.To determine whether patients with abnormal musculoskeletal US have better clinical response to glucocorticoid therapy compare to patients with normal musculoskeletal ultrasound (criterion validity, USEFUL study)	(7)USEFUL Study: prediction of response using baseline ultrasound

Chapter 4: General Methods

4.1 Ethical approvals

All patients provided written informed consent and these studies were conducted in accordance with the principles of the Declaration of Helsinki. For USEFUL study, ethical and HRA approval was gained from the North West - Greater Manchester Central Research Ethics Committee (16-NW-0060). The University of Leeds was contracted with the administrative sponsorship. Ethical approval for studies in chapters 5, 6 and 9 was gained from Yorkshire and The Humber, Leeds East Research Ethics Committee [10/H1306/88] as part of the Connective Tissue Disease and Vasculitis Cohort Cross-sectional and Longitudinal Clinical and Basic Science Evaluation (CONVAS) data collection protocol. The University of Leeds was contracted with the administrative sponsorship. The CONVAS study is an observational study based on routine clinical care that allows for collection of clinical data imaging and biomarkers on patients with a broad range of connective tissue diseases.

4.2 Clinical variables

Patients with SLE and arthritis may have disease activity purely in their joints, or may also have disease activity in other organs, such as the skin or kidneys. Global disease activity indices such as the SLEDAI and BILAG assess all organs, but the musculoskeletal component can be analysed separately. Likewise, some VAS scales assess the joints (e.g., patient's pain VAS), while others may assess all aspects of disease (e.g., patient's global health VAS). Haematological and immunological markers are often used to assess SLE. These correlate with the presence of arthritis, but also with disease activity in other organs. In selecting study endpoints we, therefore, selected those endpoints that were specific to arthritis. This selection is summarised in Table 4-1

Table 4-1: Selection of clinical variables

Musculoskeletal Specific Variables	Global lupus variables
Tender joint count	Physician's global disease activity VAS
Swollen joint count	Total BILAG
Patient's painful joint count	Total SLEDAI
Physician MSK disease activity VAS	LupusQoL
BILAG MSK component	L-QoL
SLEDAI MSK component	Patient's general health VAS
HAQ-DI	Patient's fatigue VAS
Patient's MSK Disease activity VAS	ESR
Patient's MSK Pain VAS	Complements: C3 and C4
Patient's EMS severity VAS	Anti-dsDNA titre
Patient's EMS duration	Immunoglobulins: IgG, IgA, IgM

VAS: visual analogue scale, BILAG: British Isles Lupus Assessment Group, SLEDAI: Systemic Lupus Erythematosus Disease Activity Index. MSK: musculoskeletal, ESR: early morning stiffness, L-QOL: Lupus Quality of Life, HAQ: Health assessment questionnaire

4.3 Physician assessments

The clinical assessments were performed by trained rheumatologists who were blinded to the ultrasound assessment.

4.3.1 *BILAG-2004-Index-last four weeks*

The BILAG-2004 [169], assesses disease activity in eight different organs/systems: general, mucocutaneous, neurological, musculoskeletal, cardiorespiratory, vasculitis, renal and haematological. A score is calculated for each system depending on the clinical features present and whether they are new, worse, the same or improving in the last four weeks compared with previously. BILAG-2004 numerical scores were calculated using the formula A=12, B=8, C=1, D/E=0 [387].

4.3.2 *Musculoskeletal BILAG*

The musculoskeletal component of the overall BILAG-2004 is of particular interest to this thesis. This domain assesses musculoskeletal activity in terms of joint swelling, deformities, tenosynovitis, loss of function and inflammatory type pain. It classifies musculoskeletal involvement into BILAG A-E.

4.3.3 *SLEDAI-2K 30 days*

The SLEDAI-2K 30 days [388] measures disease activity by weighting the importance of each system involved. It does not account for subjective symptoms such as fatigue, dysphoria, arthralgia, or myalgia. However, separate, quality of life instruments can be used for that purpose.

4.3.4 *Tender Joint Count*

Sixty-eight joints were assessed: shoulder, elbow, and wrist (radiocarpal, carpal and carpometacarpal are collectively designated wrist), metacarpophalangeal I-V, proximal interphalangeal I-V and knee. The investigator pressed on a joint sufficiently to induce pain if there is an inflammation as per the agreed and known tender joint count examination technique in inflammatory arthritis.

4.3.5 *Swollen Joint Count*

Sixty-six joints were assessed. Synovial fluid and/or soft tissue swelling, but not bony overgrowth, represents a positive result. The investigator felt joints for swelling as per the agreed and known tender joint count examination technique in inflammatory arthritis.

4.3.6 *Physician Musculoskeletal Disease Activity Assessment*

The investigator's evaluation of musculoskeletal disease activity was completed before the patient's global assessment. The investigator assessed the patient’s musculoskeletal disease activity considering not only impressions from the assessments made in the study, but also any

other information available such as inflammatory symptoms and morning stiffness. Disease activity in other organs (e.g. skin disease) did not affect this score. A100 mm visual analogue scale was used: the left end corresponds to very well (0) and the right end to very poor (100).

4.3.7 *Physician Global Assessment*

Physician global assessment was used to calculate composite response criteria (SRI and BICLA). The investigator assessed the patient's overall disease activity taking into account not only impressions from the assessments made in the study, but also any other information available. This score should reflect musculoskeletal and all other organ systems. A 100 mm visual analogue scale is used: the left end corresponds to very well (0) and the right end to very poor (100). Values were scaled to a 0 – 3 scale for the SRI calculation.

4.4 Patient reported outcome measures

4.4.1 *Patient Assessment of Musculoskeletal Pain*

The patient was asked 'What level of pain are you currently experiencing from your joints, muscles and/or tendons?' On a 100mm visual analogue scale. The left end corresponds to no pain and the right end to 'the worst imaginable pain'. The patients marked their own assessment on the scales in the case report forms by themselves by placing a single vertical line through the bar.

4.4.2 *Patient Assessment of Fatigue*

The patient was asked 'What level of abnormal fatigue (tiredness) are you currently experiencing?' on 100 mm visual analogue scales: the left end corresponds to no fatigue and the right end to 'extreme fatigue' (100).

4.4.3 *Patient Assessment of Morning Stiffness*

The patient was instructed to rate the severity of their morning stiffness on a 100mm visual analogue scale. The left end corresponds to “no extra stiffness” and the right end to “extremely severe morning stiffness”.

4.4.4 *Duration of Morning stiffness*

The patient was asked to estimate the time that elapsed between awakening and the time he/she is as flexible as he/she will be during a day involving typical activities. When did the sensation of stiffness begin to wear off? Duration in hours and minutes is recorded.

4.4.5 *HAQ Questionnaire*

A self-reported patient-oriented questionnaire to evaluate functional status.

4.4.6 *Lupus Quality of life (LupusQoL) Questionnaire*

A self-reporting 34 items specifically designed as a disease specific patient-reported outcome measures to assess the quality of life in SLE patients.

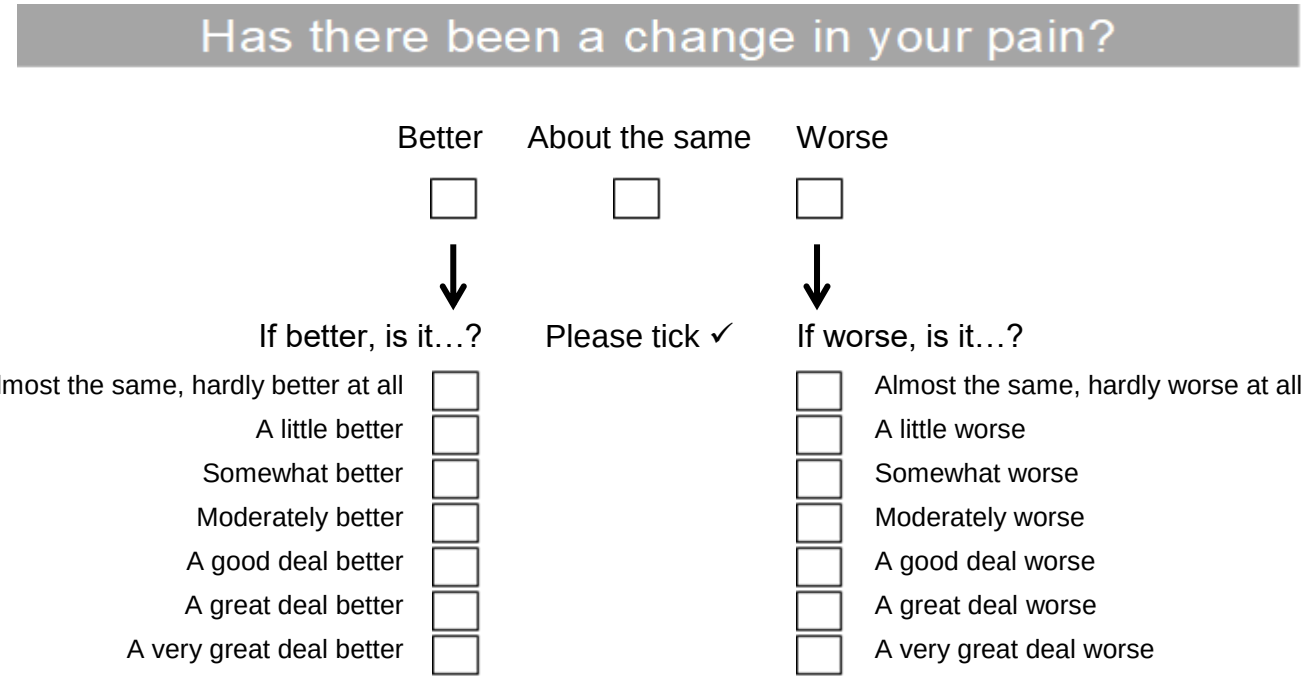
4.4.7 *SLE Quality of Life questionnaire (L-QoL)*

An alternative quality of life tool consisting of 25 statements; respondents were asked to indicate whether or not each of the statements applies to them.

4.4.8 *Likert scale for response to steroid*

15-point Likert scale (ranging from -7 to +7) to record whether they feel their symptoms have improved, worsened or remained the same since baseline.

Figure 4-1: Likert score for response to steroids



4.4.9 *Routine laboratory assessments*

Blood samples for measurement of immunological parameters were collected including ANA, anti-dsDNA, anti-ENAs (anti-sm, anti-RNP, anti-Ro, anti-La and anti-chromatin antibodies), anticardiolipin antibody (ACA), Complement levels (C3 and C4)and immunoglobulins(IgA, IgM and IgG). In addition to full blood count, renal function test, liver function test, ESR and CRP.

4.1 Musculoskeletal Ultrasound

Ultrasonography (GS and PD) was performed using high resolution ultrasound machines (HRUS). General Electric (GE) Logiq E9 HRUS with multi-linear 6-15 MHz transducer was used. Sonographers were trained and experienced in musculoskeletal ultrasound and were blinded to patient's clinical evaluation. Power Doppler was assessed with the highest gain level without background noise, PRF of 750 Hz and medium wall filter.

Bilateral wrists and hands were scanned. All joints in hand and wrists were examined using the

standard approach of examining the following; radio-carpal (RCJ), inter-carpal (ICJ), ulnar-carpal joints (UCJ) and 2nd to 5th metacarpo-phalangeal joints (MCP) and 2nd to 5th proximal inter-phalangeal joint joints (PIP). Bilateral tendon sheaths including the 1st –5th extensor tendons compartments (abductor pollicis longus and the extensor pollicis brevis tendons, extensor carpi radialis longus and extensor extensor carpi radialis brevis muscle, extensor pollicis longus, extensor digitorum and extensor indicis and extensor digiti minimi) which for the purpose of simplifying scored together as extensor tendon sheaths. The extensor carpi ulnaris was scored separately because it is commonly involved in cases of tenosynovitis. On the palmar aspect the 2nd to 5th flexor digitorium tendon sheaths were assessed for the presence of tenosynovitis.

Ultrasound abnormalities were defined according to OMERACT definitions [347]. Ultrasound findings were scored according to EULAR-OMERACT ultrasound taskforce semiquantitative 0-3 scoring system [296, 304, 389, 390]. The GS scoring was as follows; 0 = no synovial hypertrophy, 1 = mild hypertrophy, 2 = moderate hypertrophy, and 3 = severe hypertrophy. The Power Doppler scoring was as follows; 0 = absence of signal, no intra-articular flow; 1 = mild hyperaemia, one or two vessels signal (including one confluent vessel); 2 = moderate hyperaemia, (>grade 1) and less than 50% of GS area; 3 = marked hyperaemia, vessels signal in more than half of the synovial area. Tenosynovitis was defined according to the OMERACT criteria [296] and the GS and PD signal scored using a semi-quantitative 0-3 scale system (0= normal, 1=mild, 2=moderate and 3= severe) [391]. Ultrasound abnormalities (62 areas) were summarised as total grey scale (GS), PD, erosions and tenosynovitis as well as numbers of joints with abnormal GS (≥2), PD (≥1), erosions or tendons with tenosynovitis (as any GS and/or PD abnormality in the tendon sheath).

A novel composite clinical assessment tool against total ultrasound score (GSPD), combined grey scale and power Doppler scores from the hands and wrists was created to form the dependent variable in a multiple linear regression model that includes the ACR core set variables (TJC68, SJC66, patient pain VAS, patient musculoskeletal disease activity VAS, physician

musculoskeletal disease activity VAS, HAQ-DI, ESR), morning stiffness severity VAS as independent variables (8 in total). To avoid overfitting the data and to perform variable selection, penalized (Lasso) regression will be used, with cross-validation used to select optimum lambda from a grid of starting values. Baseline data will be used, at which point the level of ultrasound inflammation is expected to be highest. In a sensitivity analysis, GSPD re-calculated according to an in-house developed scoring system which updates the OMERACT-EULAR scoring system to have better measurement properties, as follows:

Table 4-2: GSPD

Original PDUS scoring

		PD			
		0	**1**	**2**	**3**
GS	**0**	0	0	0	0
	1	1	1	2	3
	2	2	2	2	3
	3	3	3	3	3

Revised PDUS scoring

		PD			
		0	**1**	**2**	**3**
GS	**0**	0	0	0	0
	1	1	1	2	2
	2	1	1	2	2
	3	1	2	2	3

4.2 USEFUL: Study Design

The USEFUL study (UltraSound Evaluation For mUsculoskeletal Lupus) is a prospective, longitudinal, multi-centre study designed to address the following unmet needs:

- Clinical problem: how can clinicians decide whether to start or increase immunosuppression for joint pain in patients with SLE?
- Outcome measures problem: what is the best outcome measure for efficacy in musculoskeletal SLE?

For the purpose of testing the prognosis and responsiveness of ultrasound in SLE a prospective study of patients with SLE and musculoskeletal symptoms receiving a commonly-used therapy of known efficacy (glucocorticoids) conducted in 7 different centers in the UK. Patient deemed by their treating physician to have inflammatory symptoms who were appropriate for therapy in an observational study were recruited. Because the change in clinical variables, or the most responsive clinical variable, is not yet known, we have chosen a 2-phase design with the internal pilot. In the first phase I used two follow up time points (2 weeks and 6 weeks) to ensure that maximal response is captured.

4.2.1 *Objectives*

Primary:

Determine whether patients with abnormal musculoskeletal ultrasound have a better clinical response to glucocorticoid therapy compared to patients with normal musculoskeletal Ultrasound.

Secondary:

- Determine whether musculoskeletal ultrasound (GS or PD) is responsive to therapy.
- Investigate the validity of a range of other clinical outcome measures against ultrasound

and clinical response.

- Assess the inter-reader reliability of ultrasound in musculoskeletal SLE

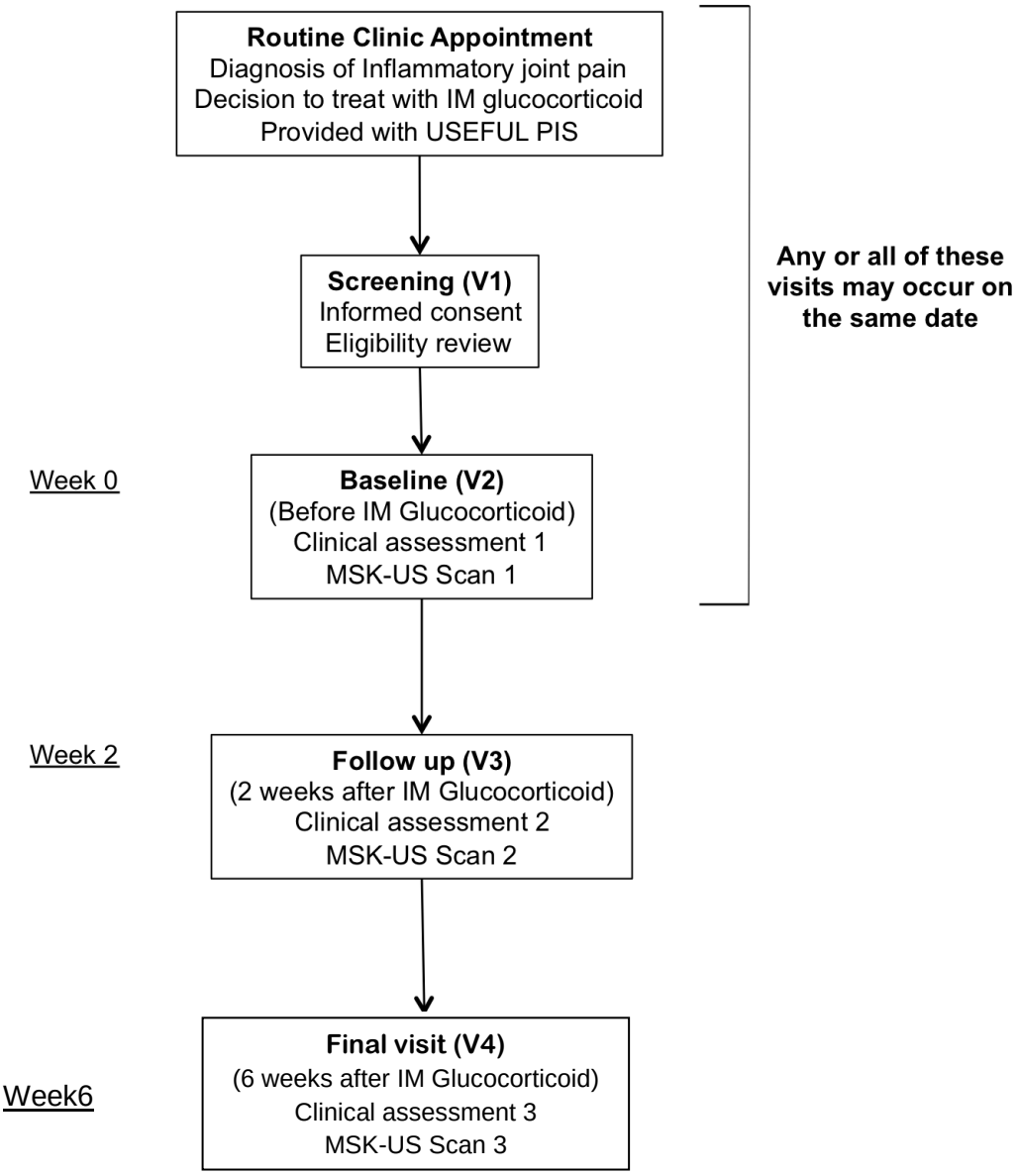
4.2.2 *Study design*

A multicenter- prospective observational study to investigate the validity of ultrasound as an outcome measure in assessing response to therapy in Systemic lupus erythematosus (SLE). Patients were treated with 120mg intramuscular methylprednisolone acetate as routine care for active musculoskeletal disease on the same date as the ultrasound and clinical assessment and then repeated at two and six weeks to assess responsiveness..

4.2.3 *Study blinding*

Sonographers were blinded to the clinical condition and therapy stage. The clinical examination and BILAG-2004 scoring were performed by investigator who were blinded to the ultrasound findings. However, patients were not blinded to therapy received as prescribed for clinical not research indication.

Figure 4-2 USEFUL study schematic:



IM: intramuscular, MSK: Musculoskeletal, PIS: Patient information sheet, US: ultrasound

Table 4-3. Summary schedule of study assessments:

Visit Week	Screen	0	2	6
Informed Consent	x			
Eligibility Criteria	x			
IM Depomedrone prescribed		x		
Physician Assessments				
Relevant medical history and demographics		x		
Relevant concomitant medications (Glucocorticoid, NSAIDs analgesia)		x		
Physician MSK diagnosis		x		
Joint Assessment (Tender and Swollen)		x	x	x
BILAG-2004		x	x	x
SLEDAI-2K		x	x	x
Physician Global Assessment VAS		x	x	x
Physician musculoskeletal disease activity VAS		x	x	x
Patient Reported Outcomes				
Patient Visual Analogue Scales (General health, musculoskeletal disease activity, pain, fatigue)		x	x	x
Morning Stiffness (VAS and minutes)		x	x	x
HAQ		x	x	x
LupusQoL and L-QOL Questionnaires		x	x	x
Patient Acceptable Symptoms State		x	x	x
Likert scale for response to glucocorticoid			x	x
Investigations				
Ultrasound examination		x	x	x
Routine clinical lab disease activity tests (U&E, LFT, FBC, ESR, PV, CRP, urine analysis)		x		x
Routine clinical lab SLE serology (dsDNA, ANA, ENA, C3, C4, Immunoglobulins)		x		
Exploratory biomarkers (serum, sample for RNA)		x	x	x

BILAG-2004: British Isles Lupus Assessment Group, HAQ: Health assessment questionnaire, L-QOL: Lupus Quality of Life, SLEDA: SLE Disease Activity Index, VAS: Visual analogue scale

4.2.4 *Inclusion criteria:*

- Patients with systemic lupus erythematosus who meet ACR/SLICC 2012 criteria.
- Patients with musculoskeletal symptoms deemed by the clinician to represent active SLE (patients need not have clinical synovitis but must have evidence to support inflammatory cause of symptoms (e.g. morning stiffness, raised inflammatory markers and no more likely alternative diagnosis for these symptoms such as osteoarthritis).
- Planned treatment with intramuscular glucocorticoids (this is typically expected to be 120mg Depo-medrone as the most commonly used preparation and dose, but clinicians may choose to use an alternative preparation or dose that they consider equivalent for that patient).

4.2.5 *Exclusion criteria:*

- Patients who ever have immunological evidence of rhupus (positive for anti-CCP antibodies or Rheumatoid Factor).
- Patient who is receiving an NSAID within 3 days prior to the intended baseline US date.
- Patient who is receiving daily oral glucocorticoid greater than prednisolone 5mg (or equivalent), or have received IV/IM glucocorticoid in the past 3 months.
- Treated with rituximab or cyclophosphamide in the past 6 months.
- Any changes in immunosuppressant therapy /dose in the last three months.

4.2.6 *Withdrawal criteria*

Patient discontinued from the study if he/she was withdrawn his/her consent. The investigator may withdraw a patient from the study for any other reason that threatens patient safety or the integrity of study data. Patients who did not attend the baseline visit were withdrawn. Patients who completed the baseline visit were permitted to complete the study if they missed one of the other visits.

4.2.7 *Inter reader reliability for USEFUL study*

The inrter-reader reliability was assessed using the quadratic-weighted Kappa static for the semi-qualitative measurements. Values of Kappa less than 0.4 were considered as poor agreement, values between 0.4 and 0.75fair to good, and >0.75 were considered as excellent agreement[392]. All sonographers from the study centres attended a training day before the start of the study. They participated in an inter-reader reliability exercise where they scanned four patients' joints (17 areas) and joint by joint and overall all agreement were calculated. The ranges of kappa values for Grey scale was between 0.38 and 0.85 and the overall kappa agreement for Power Doppler and erosion were 0.98 and 0.85 respectively. Generally, the agreement between the sonographers was good.

Table 4-4: Ultrasound reliability

Site	Overall Kappa
GS	
ECU	0.65
ETS	0.80
FT2	0.80
FT3	0.72
FT4	0.83
FT5	0.85
ICJ	0.38
MCP2	0.60
MCP3	0.65
MCP4	0.63
MCP5	0.55
PIP2	0.78
PIP3	0.65
PIP4	0.80
PIP5	0.82
RCJ	0.58
UCJ	0.65
All	0.69
PD	
All	0.98
E	
All	0.85

4.3 Interim Analysis for USEFUL study

We planned an interim analysis to decide the power for the main study. We needed to determine which of the clinical variables (e.g. tender joint counts or VAS) was most strongly correlated with patient-reported change in pain. That variable would be used to compare improvement in patients with or without ultrasound at baseline. These data can then be used to power the primary endpoint.

After the first 70 patients have completed 6 weeks follow-up, the rate of ultrasound activity (presence of any joint scoring GS≥2 and/or PD≥1) at baseline have been calculated at the group level. Changes in each of the candidate primary outcomes have been correlated with the Likert scores for response to therapy at both 2 and 6 weeks. The candidate outcome with the strongest association was selected as the primary outcome; the visit at which the strongest association is identified was selected as the primary endpoint. The baseline mean and follow-up standard deviation of the chosen outcome calculated in all patients were used to calculate a revised sample size, taking into account the estimated rate of ultrasound activity.

For the musculoskeletal domains of the existing measures BILAG (2004) and SLEDAI-2K, changes at 2 and 6 weeks were recorded as improved, same or worse. This is because these variables show little scope for change; SLEDAI-2K can only take the values 0 or 4, whilst BILAG (2004) domains A-E can be assigned values 12, 8, 1, and 0 respectively.

4.3.1 *The results of the Interim analysis:*

The pilot phase analysis included the first 70 patients. Of the candidate primary outcomes, at both week 2 and 6, EMS VAS was the most strongly correlated with patient-reported change in pain (Table 4-5). The correlation was strongest at week 2. This was also the case for EMS (minutes) and patient-reported painful joint count; for the remaining variables, stronger associations were found at week 6 than week 2.

Deviation from the planned analysis: Although the statistical analysis plan stated that bootstrapped confidence intervals for the differences in correlations between variables would be presented, this has not been possible. In some bootstrapped samples the imputation model failed, due to the large number of parameters being estimated relative to the number of patients in the pilot phase. However, the imputation model in the main sample was successful. The lack of confidence intervals does not affect the definition of the primary outcome, which was intended to be based on the maximum observed point estimate of the correlation.

4.3.2 *Implications for the main trial*

The primary endpoint for the main trial will be EMS VAS (mm) at 2 weeks; EMS VAS at 6 weeks, and the remaining candidate variables at both 2 and 6 weeks were deemed secondary endpoints. In terms of study statistical power calculation; at alpha=0.05, 1-Beta=0.8 it required 130 patients in total to show a difference of 20% of the baseline value in EMS VAS at 2 weeks between those with active ultrasound in at least one joint and those without active ultrasound (Table 4-6).

Table 4-5: Kendall's tau-a correlations with patient-reported change in pain:

Variable	W2	W6	W2 - W6	cf. EMSVAS W2	cf. EMSVAS W6
TJC68	-0.036	0.154	-0.190	0.328	0.006
SJC66	-0.070	0.125	-0.195	0.362	0.034
Physician MSK DisAct VAS	0.049	0.117	-0.068	0.243	0.042
SLEDAI MSK	0.053	0.157	-0.104	0.239	0.002
BILAG MSK	0.021	0.150	-0.129	0.270	0.009
HAQ-DI	0.062	0.124	-0.062	0.230	0.036
Patient MSK DisAct VAS	0.117	0.153	-0.036	0.174	0.007
MSK Pain VAS	0.232	0.088	0.145	0.059	0.072
EMS VAS	0.291	0.159	0.132	-	-
EMS mins	0.279	0.070	0.209	0.012	0.089
Painful Joint Count	0.135	0.147	-0.011	0.156	0.013

TJC: tender joint count, SJC: swelling joint count, EMS: early morning stiffness, BILAG: British Isles Lupus Assessment Group, SLEDAI: Systemic Lupus Erythematosus Disease Activity, HAQ: Health assessment questionnaire, VAS: visual analogue Scale, MSK: musculoskeletal

Table 4-6: Sample size calculation:

Alpha	0.05
Power	80%
Mean EMS BL (n=70)	70.40
Mean EMS BL (n=70) minus 20%	56.32
Standard deviation of EMS at 2 weeks	28.16
Proportion US active (n/70)	0.59 (41)
Ratio %inactive:%active	0.71
Correlation (r) EMS VAS BL vs 2 weeks	0.31
Total required (unadjusted)	**130**
Total required adjusting for correlation and 10% dropout **((1-(r squared))*(N))*(1/0.9)**	**130**

EMS: early morning stiffness, VAS: visual analogue scale, US: ultrasound

4.4 USEFUL Full Study population overview

A total of 133 consecutive patients were recruited (126 females and 7 males) in seven centres (Table 4-7). The majority of patients were recruited in Leeds. Baseline demographic data are shown in Table 4-8. The mean age was 46.1, range 17-78 and standard deviation 13.5. The vast majority of the patients were white (62%) followed by South Asian (26%), 11% were black and 2% had another ethnicity.

Table 4-7. Recruitment summary:

Center	Number of patients
Leeds	107
Bradford	10
Doncaster	7
Southampton	3
UCL	2
King's	2
Blackburn	2

Table 4-8: Demographics USEFUL (full study)

	All patients	US activity at baseline		Difference (95% CI)	Test statistic, P value
		Inactive	Active		
	N=133	N=55	N=78		
Age (years) Mean (SD), range	46.1 (13.5), 17.0 to 78.0	47.9 (12.3), 25.0 to 76.0	44.8 (14.3), 17.0 to 78.0	3.1 (-1.6, 7.8)	t=1.32, p=0.190
Median (IQR)	47.0 (35.0, 55.0)	50.0 (36.0, 57.0)	45.0 (34.0, 54.0)		
Disease duration (y) Mean (SD), range	9.3 (8.9), 0.1 to 40.0	10.2 (9.8), 0.1 to 40.0	8.7 (8.1), 0.1 to 35.0	1.5 (-1.6, 4.5)	t=0.93, p=0.352
Median (IQR)	6.0 (2.0, 15.0)	7.0 (2.0, 17.0)	5.0 (2.0, 15.0)		
Sex n/N (%)					chisq=5.21, p=0.022
Male	7/133 (5)	0/55 (0)	7/78 (9)		
Female	126/133 (95)	55/55 (100)	71/78 (91)		
Ethnicity n/N (%)					chisq=6.06, p=0.195
White	82/133 (62)	40/55 (73)	42/78 (54)		
South Asian	34/133 (26)	11/55 (20)	23/78 (29)		
Black	14/133 (11)	3/55 (5)	11/78 (14)		
East Asian	1/133 (1)	0/55 (0)	1/78 (1)		
Other	2/133 (2)	1/55 (2)	1/78 (1)		

SD: standard deviation, IQR: interquartile range

4.4.1 *Baseline clinical characteristics*

Antimalarial medication (Hydroxychloroquine) was used in 89/133 patients (66%). Forty (40/133) patients (30%) received oral immunosuppressant with or without hydroxychloroquine (Methotrexate = 16, Azathioprine = 11, Mycophenolate mofetil = 13). 31/133(23%) were on low-dose glucocorticoid(less than 5 mg prednisolone or equivalent). 27/133(20%) were receiving NSAID (which stopped at least three days before the scan). Rates of -musculoskeletal-BILAG abnormalities in the musculoskeletal study group were; BILAG A: 14/133(11%); BILAG B: 52/133(39%); BILAG C: 65/133(49%). Overall, 78/133(58.6%) patients had abnormal ultrasound findings during the baseline visit and 55/133(41.4%) had normal ultrasound scan. More details on baseline characteristics are given in the results of chapters 7 and 8.

4.4.2 *Symptoms and signs of other musculoskeletal diseases*

As it is often confusing to the assessor if the pain is due to SLE or other conditions such as fibromyalgia or osteoarthritis, assessors were asked about their opinion of the musculoskeletal diagnoses (tick lists – Yes/No or free text)

- Inflammatory features: EMS, distribution, symmetry, swelling, serology, other SLE features, and prior therapy response.
- Fibromyalgia features: Fatigue, waking un-refreshed, cognitive symptoms, somatic symptoms, and consultant's overall opinion.
- Osteoarthritis features: Hard tissue enlargement of two or more selected joints, hard tissue enlargement of DIPs, deformities consistent with OA, previous radiographic evidence in symptomatic sites, consultant overall opinion.

32/133 patients were judged by the assessor to have fibromyalgia of whom 18/32 had abnormal ultrasound scan. In terms of osteoarthritis, the assessor said 36/133 had osteoarthritis of them 20/36 OA patients had abnormal ultrasound scan (GS or PD).

4.4.3 *Patient disposition*

In week 2 visit, 122 patients attended (2 withdrawn, 5 did not attend and 4 lost follow up). In week 6 visit 121 attended (three withdrawn, three did not attend and five patients lost their follow up). The main cause of patients withdrawn was the need to start other treatments which were not permitted in the study protocol Table 4-9.

Table 4-9: Retention of patients in USEFUL (full study)

	All patients N=133
Baseline	
Attended	133/133 (100)
Week 2	
Attended	122/133 (92)
Withdrawn	2/133 (2)
Did not attend	5/133 (4)
Lost to follow-up	4/133 (3)
Week 6	
Attended	121/133 (91)
Withdrawn	4/133 (3)
Did not attend	3/133 (2)
Lost to follow-up	5/133 (4)

Chapter 5: Cross-Sectional Study: Defining Musculoskeletal Manifestations in Systemic Lupus Erythematosus

5.1 Introduction:

Defining active disease in systemic lupus erythematosus is challenging for both clinical trials and routine practice. In clinical trials, the difficulty with defining active disease has been illustrated by a series of recent negative trials of promising new treatments. For example, in the belimumab programme, a negative phase II trial was followed by positive phase III data after the target population and primary endpoints were revised [154]. In routine practice, there is an increasing emphasis on defining active disease. First, because of the need to decide on biologic prescription. Second, for treat-to-target strategies that aim to treat to a target of low disease activity while minimizing glucocorticoid exposure [393].

Inflammatory musculoskeletal (MSK) symptoms are common in SLE, being the first presenting symptom in around 50% of cases and affecting up to 95% of patients at some point[124, 158]. Joint pain in SLE has a great impact on quality of life and results in loss of function [7, 124, 394]. Accordingly, musculoskeletal disease is a common reason for inclusion in clinical trials. For example, in the phase III ILLUMINATE study, at baseline 81% of patients had musculoskeletal activity defined by the SLE Disease Activity Index (SLEDAI) [395].

Currently, musculoskeletal disease activity is defined using musculoskeletal items in the SLEDAI [396] and BILAG (BILAG 2004) [169]. Although both are validated, there are face validity problems with these tools. They were designed to assess multi-organ system disease and therefore capture less detail on an individual organ system compared with organ-specific instruments such as the DAS28 used in RA [397]. For example, SLEDAI scores four points for arthritis affecting two or more joints and none for lesser degrees of arthritis. Therefore,

there is no difference in score between a swollen joint count of 28 and two. Joints are considered affected if there is tenderness, warmth, swelling or effusion. The BILAG index allows differentiation of severe synovitis (BILAG-A), moderate synovitis (BILAG-B) and inflammatory arthralgia (BILAG-C), as well as reduction of A and B scores to B and C respectively if symptoms are improving. Importantly, because of the need to assess a wide spectrum of symptoms in SLE, assessors must determine whether features are due to SLE or another pathology for both indices.

Modern imaging has brought a greater understanding to RA and explained the discrepancies in clinical and objective imaging-defined synovitis. In low disease activity states, such as early arthritis or remission, musculoskeletal ultrasound-detected synovitis has been shown to explain the long-term adverse consequences [398, 399].

Data on musculoskeletal ultrasound in SLE are limited and also ultrasound is not commonly used in practice or trials. In a systematic review, we found that several studies reported ultrasound -detected abnormalities in SLE but were inconsistent with their reported prevalence of abnormality[121]. Probably due to methodological differences such as failure to clearly separate rhupus from 'pure' SLE, controlling for NSAIDs and glucocorticoids, and reporting OMERACT criteria. Furthermore, no study has confirmed the clinical significance of ultrasound synovitis.

I therefore studied a large cohort of patients with objective measures of synovitis in order to define the population of patients who should be included in clinical trials and receive escalation, tapering or avoidance of glucocorticoids, conventional and biologic therapies in routine practice. In order to be able to estimate the prevalence of each clinical and ultrasound presentation in a general SLE population, I recruited unselected, consecutive patients with inflammatory musculoskeletal symptoms. I addressed the issues with previous ultrasound studies by controlling for rhupus, NSAID and glucocorticoid therapy and reporting OMERACT grades of abnormality.

5.2 Hypothesis

There is a considerable proportion of SLE patients with objective (ultrasound detected) musculoskeletal inflammation that is symptomatic but not detected by existing clinical instruments.

5.3 Objective

To evaluate a cross-sectional cohort of consecutive Systemic Lupus Erythematosus patients with musculoskeletal symptoms for both clinical and ultrasound synovitis, and determine the clinical associations of subclinical synovitis.

5.4 Patient and Methods

A cross-sectional observational study was conducted in one hundred and twelve consecutive SLE patients with active inflammatory musculoskeletal symptoms in two UK centres (Leeds and Southampton). Eighty-eight consecutive patients with inflammatory musculoskeltal symptoms and 24 asymptomatic SLE controls were recruited. Patients had different clinical assessments (BILAG, SLEDAI, joint counts, patient and physician visual analogue score), routine laboratory tests and ultrasound of two hands and wrists.

Inclusion criteria were:

1. Meet ACR/SLICC criteria for SLE.
2. Musculoskeletal symptoms deemed by the investigator to represent active SLE (patients need not have clinical synovitis but must have evidence to support inflammatory cause of symptoms (e.g. morning stiffness, raised inflammatory markers and no more likely alternative diagnosis for these symptoms such as osteoarthritis).
3. Stable dose of immunosuppressant therapy in the past six weeks (methotrexate, mycophenolate mofetil, mycophenolic acid, azathioprine, cyclosporine, cyclophosphamide, intravenous immunoglobulin, belimumab or other regular biologic therapy).

4. A cohort of patients who had SLICC diagnostic criteria for SLE but no current inflammatory musculoskeletal symptoms (MSK-BILAG D or E) were recruited as a control group.

Exclusion criteria

1-Patients were excluded if they had immunological evidence of rhupus (positive for anti-CCP antibodies or Rheumatoid Factor) ever.

2-Had received an NSAID within three days prior to the intended baseline ultrasound date

3-Hd received daily glucocorticoid greater than prednisolone 5mg (or equivalent), or have received IV/IM glucocorticoid in the past three months.

Patients with improving disease were excluded. This allowed grouping of symptomatic patients into clinically comparable three BILAG categories: severe clinical synovitis with loss of function (musculoskeletal (MSK) BILAG A), mild to moderate synovitis (MSK-BILAG B), inflammatory symptoms but no synovitis (MSK-BILAG C).

5.5 Ethical Approval:

All individuals provided informed written consent and this research was carried out in compliance with the Declaration of Helsinki. All procedures were performed in accordance with relevant guidelines and regulations. The University of Leeds was contracted as administer sponsorship.

5.6 Clinical assessment

Clinical assessments were performed by rheumatologists blinded to the ultrasound assessment with training and experience in relevant indices. Overall disease activity was assessed using BILAG-2004, SLEDAI-2K and damage was assessed using the SLICC (SLICC-DI). Musculoskeletal components of BILAG-2004 and SLEDAI-2K were summarized separately as MSK-BILAG (A-E) and MSK-SLEDAI (0 or 4 points) for analyses. Joint disease was also assessed using 66/68 tender and swollen joint counts, symptomatic joint count,

physician global visual analogue score (VAS, 0–100 mm) and patient's disease activity VAS (0–100 mm) and DAS28-ESR (four variables).

5.7 Ultrasound assessment:

Ultrasound was performed using high resolution ultrasound machines; General Electric (GE Healthcare, Chicago, IL) Logiq E9 ultrasound with multi-linear 6–15 MHz transducer in Leeds and Esaote (Genoa, Italy) MyLab 70. Ultrasound with multi-linear 5.0–13.0 MHz transducer in Southampton. All sonographers (one in Southampton and two in Leeds) were trained in musculoskeletal ultrasound and blinded to clinical status. Power Doppler was assessed with the highest gain level without background noise, pulse repetition frequency of 750 Hz and medium wall filter.

5.8 Laboratory assessment:

Different laboratory tests were done and that included C-Reactive Protein (CRP) (mg/l), Erythrocyte Sedimentation Rate (ESR) (mm/h), Rheumatoid Factor(RF) (IU/ml), Cyclic Citrullinated Peptide(CCP) antibodies (CCP, IU/ml), complements (C3 and C4, g/l), Anti-nuclear Anti-body(ANA), Extracted Nuclear Antibodies including anti-dsDNA, anti Ro, anti La, anti-chromatin, anti Sm, anti-RNP (using Bioplex 2200) and immunoglobulins (IgA, IgM, IgG, using nephelometry) were measured on the same day of the visit in an accredited clinical diagnostic laboratory.

5.9 Statistical analysis

Patients were classified according to BILAG groups (MSK-BILAG=A, B, C and D/E) and SLEDAI groups (MSK-SLEDAI = 0 or 4 points). Overall clinical characteristics (demographics, therapies, clinical joint assessments and immunological parameters) and ultrasound characteristics were summarized for each group using proportions of patients or median and interquartile range as appropriate. Ultrasound abnormalities were calculated as total GS, PD, erosions and tenosynovitis as well as numbers of joints with abnormal GS ($\geqslant$2), PD ($\geqslant$1), erosions or tenosynovitis (as any GS and/or PD abnormality in the tendon sheath).

Association of BILAG grade and erosions with patient groups were tested using Fisher's exact test. Level of agreement between clinical assessment and ultrasound when detecting synovitis was quantified as the proportion of joints in which both methods exactly agreed over the presence or absence of synovitis (percentage exact agreement [PEA]), proportions of category-specific negative and positive agreement (Sp0 and Sp1 for absence and presence of synovitis, respectively), and the proportions of joints where clinical examination (CE) and ultrasound disagreed in either direction (US>CE, US<CE). The Category-specific agreement was defined as the proportion of the total number of positive or negative ratings (CE=US) that were concordant; it represents the conditional probability that ultrasound would place a patient in category X, given than CE had placed them in that category and vice versa. The kappa statistic was also calculated and supplemented with the prevalence-adjusted bias-adjusted kappa to give an indication of the extent to which differences in the overall level of synovitis identified by each assessment method together with imbalances in the proportions of joints with and without synovitis affected the calculated value of kappa.

Patients with inflammatory symptoms without clinical joint swelling (MSK-BILAG-C) were divided into 'subclinical synovitis' and 'normal' groups based on: GS $\geqslant$ 2 in $\geqslant$1 joint; PD $\geqslant$1 in $\geqslant$1 joint; GS $\geqslant$ 1 or PD $\geqslant$ 1 in $\geqslant$ 1 tendon sheath. For each abnormality, we compared: clinical (patient- and physician-VAS, tender and symptomatic joint count, DAS28-ESR); immunological parameters that differed in BILAG groups (total serum IgG, ESR); and ultrasound erosions, using Mann–Whitney-U tests.

All tests were conducted at a two-sided 5% level of significance. Statistical analyses were performed using IBM SPSS Statistics v24.

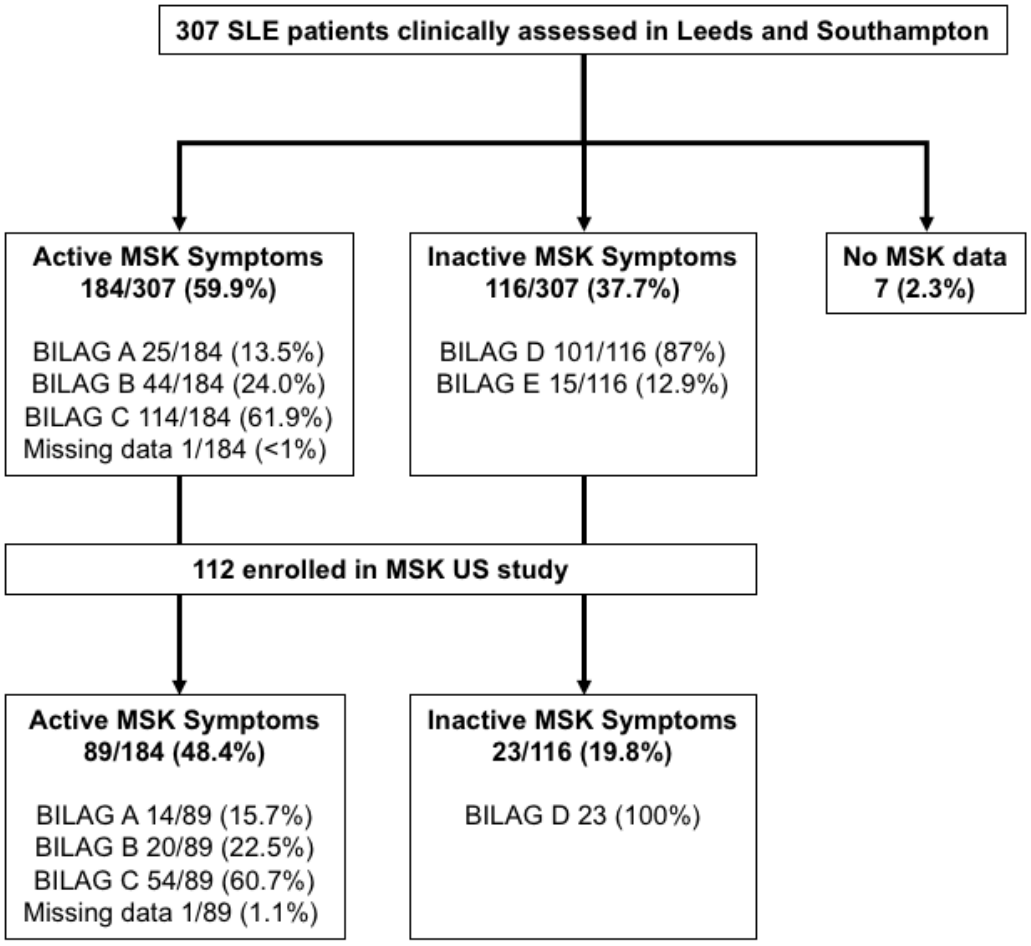
5.10 Results

5.10.1 *Recruitment*

In order to be able to estimate the prevalence of each clinical and ultrasound presentation in a general SLE population, our group recruited unselected, consecutive patients with

inflammatory musculoskeletal symptoms. 307 patients enrolled in observational research studies were clinically assessed.

Figure 5-1. Recruitment flow chart:



5.10.1.1 Patient characteristics

Patient recruitment is shown in Figure 5-1 of consecutive patients clinically assessed, 184 had musculoskeletal symptoms deemed to be inflammatory. Rates of BILAG abnormality in the overall group were BILAG A: 25/184 (13.5%); BILAG B: 44/184 (24%); BILAG C: 114/184 (61.9%). A further 116 patients had no active musculoskeletal symptoms (101 with previous involvement recorded, 87%). There were 112 consecutive SLE patients recruited into the musculoskeletal study (Leeds: 92; Southampton: 20). These included 89 consecutive patients with active musculoskeletal symptoms who consented to participate. We also recruited 23 of the patients with prior musculoskeletal involvement. All 100% were

ANA positive. They were predominantly female (108/112, 96%). Median (interquartile range) age was 46.5 (34, 57) and disease duration 60 (24, 168). Median SLICC damage index was 0 (0, 1). There were 46/112 patients (41%) treated with HCQ alone and 43/112 (38%) received oral immunosuppressant with or without HCQ (methotrexate = 15, azathioprine = 10, mycophenolate mofetil = 18). Thirteen had received previous rituximab and 42/112 were on low-dose glucocorticoid. Rates of -MSK-BILAG abnormalities in the musculoskeletal study group were very similar to the overall group: BILAG A: 14/89 (15.7%); BILAG B: 20/89 (22.5%); BILAG C: 54/89 (60.7%). Other baseline demographics and clinical characteristics are presented in Table 5-1

Table 5-1. Clinical and serological characteristics according to musculoskeletal disease status:

	All Patients	Patients with MSK Symptoms					No MSK Symptom
		BILAG			SLEDAI		
		MSK-BILAG=A	MSK-BILAG=B	MSK-BILAG=C	MSK-SLEDAI=4	MSK-SLEDAI=0	MSK-BILAG=D and MSK-SLEDAI=0
No. of patients	112*	14	20	54	28	61	23
Disease duration	60 (24,168)	36 (12,180)	36 (18,180)	84 (24,168)	84 (24,168)	51 (21.5,168)	108 (53.3,171)
Age mean(range)	46.5 (34,57)	49 (36,59)	46.5 (33,55)	49 (37.5,58)	45 (18,73)	41.5 (31.2,51.7)	35 (26,53)
Therapy							
Steroid, N (%)	42/112 (38%)	3/14 (21%)	10/20 (50%)	17/54 (30%)	19/28 (68%)	38/61 (62%)	12/23 (52%)
HCQ only, N (%)	55/112 (49%)	7/14 (50%)	9/20 (45%)	32/54 (58%)	15/28 (54%)	33/61 (54%)	7/23 (30%)
Oral Immunosuppressant, N (%)	42/112 (38%)	4/14 (29%)	9/20 (45%)	20/54 (36%)	9/28 (32%)	24/61 (39%)	9/23 (31%)
Rituximab, N (%)	22/112 (20%)	2/14 (14%)	2/20 (10%)	5/54 (9%)	3/28 (11%)	6/61 (10%)	4/23 (17%)
Clinical Assessment							
TJC	5 (1,11)	9 (5,18)	7(2,13)	7 (2,12)	5 (9,13)	6 (2,12)	0 (0, 0)
SJC	0 (0,2)	4 (3, 9)	2 (1,2)	0 (0,0)	3(2,5)	0(0,0)	0 (0, 0)
Patients arthritis VAS	50 (24,70)	70 (40,84)	57 (46, 70)	50 (40,70)	63 (43,77)	20 (8.5,31)	0 (0, 22)
Physician VAS	20 (3,50)	67 (55, 76)	50 (32, 60)	15 (7, 22)	60 (35,70)	50 (40,70)	0 (0, 0)
Symptomatic joints	5 (0,13)	10 (5,20)	9 (2,17)	7 (2,13)	10 (5,17)	6.5 (1,13)	0 (0, 0)
Total SLEDAI	4 (0,6)	6 (4,8)	6.0 (4, 8)	2 (0, 5.5)	6 (4,8)	5.5 (4, 8)	0(0, 2)
SLICC-DI	0 (0,1)	0 (0, 1)	0 (0, 1)	0 (0, 0)	0 (0,0)	0(0,1)	0 (0, 0)

	All Patients	Patients with MSK Symptoms					No MSK Symptom
		BILAG			SLEDAI		
		MSK-BILAG=A	MSK-BILAG=B	MSK-BILAG=C	MSK-SLEDAI=4	MSK-SLEDAI=0	MSK-BILAG=D and MSK-SLEDAI=0
CRP	5 (5,8)	5 (5,11)	5 (5,10)	5 (5,10)	5 (5,15)	5 (5,7.5)	5 (5, 5)
ESR	20 (9,42)	47 (11,81)	31 (12,42)	14 (9,40)	32 (10,58)	16 (9,41)	12 (4,23)
Serology							
IgG	12.6 (9.7,17.5)	13 (10,20)	18 (9,21)	12.7 (11,15)	14 (11,20)	12.5 (10,16)	11 (9,16.5)
Raised Anti-dsDNA, N (%)	36/108 (33%)	6/14(43%)	5/18 (28%)	16/52 (31%)	8/27 (30%)	19/58(33%)	8/23 (35%)
Low C3, N (%)	11/104 (11%)	3/14 (21%)	5/15 (33%)	8/52(15%)	20/28 (71%)	3/58 (5%)	7/22 (32%)
Low C4, N (%)	20/104 (19%)	2/11 (17%)	4/14 (21%)	8/49 (16%)	18/28 (64%)	7/58 (12%)	8/20 (36%)

All values presented are median (1stQuartile, 3rd Quartile) unless otherwise stated. SLICC-DI = SLICC damage index. *1 patient with missing BILAG/SLEDAI data was excluded from further analysis. BILAG: British Isles Lupus Assessment Group: SLEDAI: Systemic Lupus Erythematosus Disease Activity, TJC: tender joint count. SJC: swollen joint count, CRP, ESR: erythrocyte sedimentation rate

Table 5-2. Frequencies of different US abnormalities in BILAG and SLEDAI groups:

	All patients (n=112)	Patients with MSK symptoms					No MSK symptom
		BILAG			SLEDAI		
		MSK-BILAG=A (n=14)	MSK-BILAG=B (n=20)	MSK-BILAG=C (n=54)	MSK-SLEDAI = 4 (n=28)	MSK-SLEDAI = 0 (n=61)	MSK BILAG=D (n=23)
Overall Synovitis (GS ≥ 2 and/or PD≥1)	57%	100%	85%	53%	86%	52%	17%
Total PD synovitis	39%	100%	65%	30%	79%	36%	4%
Total mod-severe PD synovitis	26%	100%	35%	13%	64%	26%	4%
Total erosions	9%	29%	20%	4%	25%	4.8%	100%
Tenosynovitis	25%	57%	35%	24%	43%	21%	0%
Hands synovitis	57%	100%	85%	52%	86%	67%	17%
Hands mild PD synovitis	50%	100%	75%	44%	86%	55%	9%
Hands mod-severe PD synovitis	29%	93%	50%	15%	64%	31%	0%
Hand erosions	13%	29%	20%	11%	29%	12%	0%
Hands tenosynovitis	18%	57%	30%	11%	39%	19%	0%
Feet synovitis	27%	44%	20%	26%	43%	19%	22%
Feet mild PD synovitis	9%	14%	13%	13%	7%	12%	0%
Feet mod-severe PD synovitis	2%	14%	0%	0%	2%	0%	0%
Feet erosions	5%	7%	10%	4%	7%	5%	4%
Total GS score, median (1st, 3rd Q)	4(1,15)	27 (19, 41)	11 (4, 20)	3.5(1, 7.25)	3(1,8)	4(1, 11)	2 (0, 6)
Total PD score, median (1st, 3rd Q)	0(0,3)	13.5 (6, 26)	1 (0, 6.8)	0 (0, 1)	0(0,1)	0(0,2.3)	0 (0, 0)
Total Erosion score, median (1st, 3rd Q)	0(0,0)	0 (0, 2)	0 (0, 1)	0(0,0)	0(0,0)	0(0,0)	0 (0, 0)
Total TS GS score, median (1st, 3rd Q)	0(0,0)	0 (0, 3)	0 (0, 0)	0(0,1)	0(0,0)	0(0,0)	0 %

	All patients (n=112)	Patients with MSK symptoms					No MSK symptom
		BILAG			SLEDAI		
		MSK-BILAG=A (n=14)	MSK-BILAG=B (n=20)	MSK-BILAG=C (n=54)	MSK-SLEDAI = 4 (n=28)	MSK-SLEDAI = 0 (n=61)	MSK BILAG=D (n=23)
Total TS PD score, median (1st, 3rd Q)	0(0,0)	0 (0, 2)	0 (0, 0)	0(0,0)	0(0,0)	0(0,0)	0 (0,0)
% PD score of 1 in hands	37%	86%	60%	30%	68%	36%	0%
% PD score of 2 in hands	29%	93%	50%	15%	64%	31%	0%
% PD score of 3 in hands	9%	36%	10%	4%	21%	7%	0%
% Erosion=1 in hands	12%	21%	20%	11%	29%	10%	0%
% Erosion=2 in hands	5%	14%	15%	2%	14%	2%	0%
% Erosion=3 in hands	2%	7%	5%	0%	1%	2%	0%

All values presented as % of patients unless otherwise stated. BILAG: British Isles Lupus Assessment Group: SLEDAI: Systemic Lupus Erythematosus Disease Activity .GS: gray scale, PD: power Doppler.

GS scoring was as follows; 0 = no synovial hypertrophy, 1 = mild hypertrophy, 2 = moderate hypertrophy, and 3 = severe hypertrophy. The PD scoring was as follows; 0 = absence of signal, no intra-articular flow; 1 = mild hyperaemia, one or two vessels signal (including one confluent vessel); 2 = moderate hyperaemia, (>grade 1) and less than 50% of GS area; 3 = marked hyperaemia, vessels signal in more than half of the synovial area [296, 309] The erosion scoring was as follows; 0 = no erosion, 1 = small erosion/ minimal bone surface area affected <1/3 of joint quadrant, 2 = moderate size erosions/ moderate bone surface area affected <2/3 of joint quadrant hypertrophy, and 3 = large size erosion/ severe bone surface area affected ≥2/3 of joint quadrant)[308].

5.10.2 Most symptomatic patients do not have clinical synovitis

In this consecutive series, most patients with active musculoskeletal symptoms (as defined above) did not have clinical synovitis on clinical examination (and therefore did not meet levels of BILAG and SLEDAI criteria usually required for entry into clinical trials or to start biologic therapy). Of the 88 patients deemed by clinicians to have symptoms due to active inflammatory SLE, clinical inflammation was seen defined by BILAG A or B in 38% (34/88) or defined by the SLEDAI-MSK criterion in 32% (28/88). The others were classified as BILAG-C or MSK-SLEDAI = 0.

5.10.2.1 Ultrasound revealed a large group of patients with subclinical synovitis

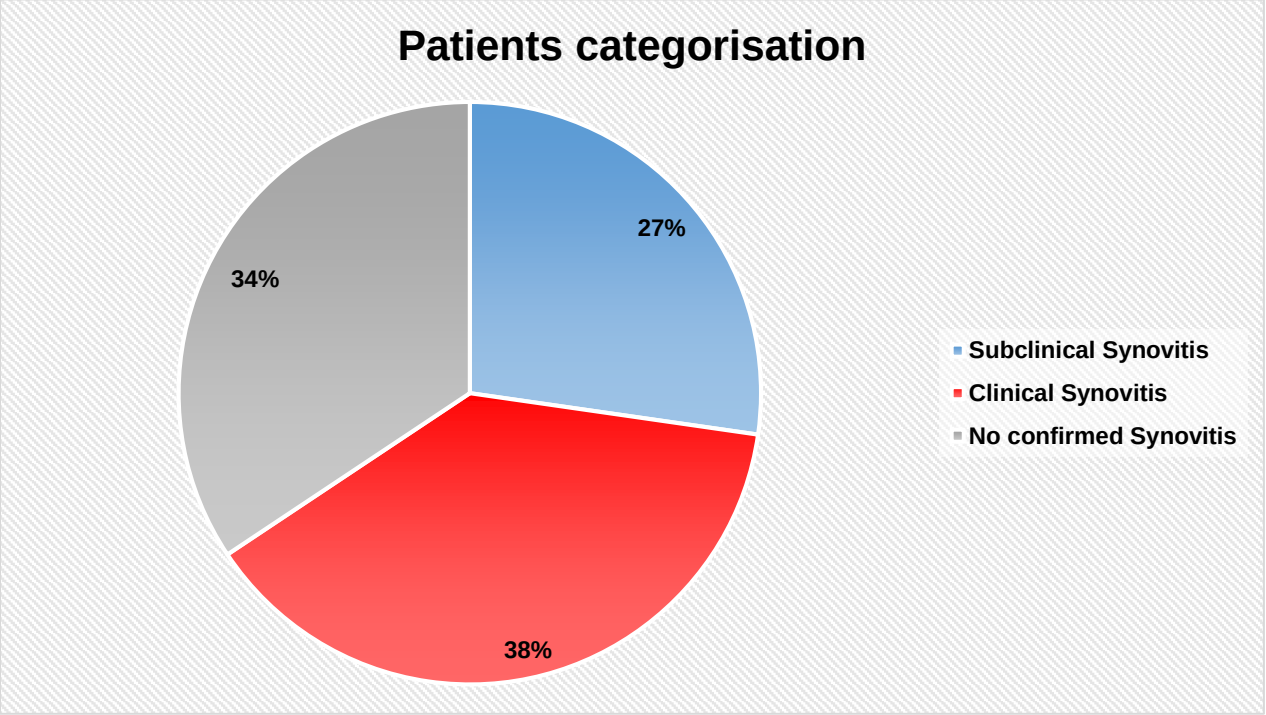
I next compared the ultrasound findings according to clinical assessment (Table 5-2). This revealed a large group of patients with subclinical synovitis confirmed on ultrasound that was not detected clinically. Overall, 68% (60/88) of symptomatic patients had ultrasound inflammation (GS $\geqslant$ 2 and/or PD $\geqslant$ 1 or tenosynovitis) compared with 17% (4/23) of asymptomatic patients. Therefore, in patients with inflammatory symptoms, I observed three major groups (Figure 5-2) (1) Clinical synovitis: (38%) 34/88 patients had one or more swollen joint, scoring BILAG A or B; (2) Subclinical synovitis (27%) 24/88 patients had no swollen joint but confirmed ultrasound abnormality; (3) No confirmed synovitis, with no swollen joint and no significant ultrasound abnormality in 30/88 (34%).

5.10.3 *Sensitivity and specificity of clinical definitions of active disease*

Overall, there was ultrasound confirmed joint inflammation defined by BILAG A or B in (38%) 34/88, defined by SLEDAI-MSK criterion (32%) 28/88; and defined by GS $\geqslant$ 2 and/or PD $\geqslant$ 1 or tenosynovitis in (61%) 54/88. Only 4/88 patients were reported to have clinical joint swelling not confirmed by Ultrasound.

BILAG A/B had sensitivity (95% CI) of 56% (41, 69%) and specificity of 89% (72, 96%). SLEDAI-MSK criterion had sensitivity of 44% (31, 59%) and specificity of 89% (72, 96%

Figure 5-2 Patients categories



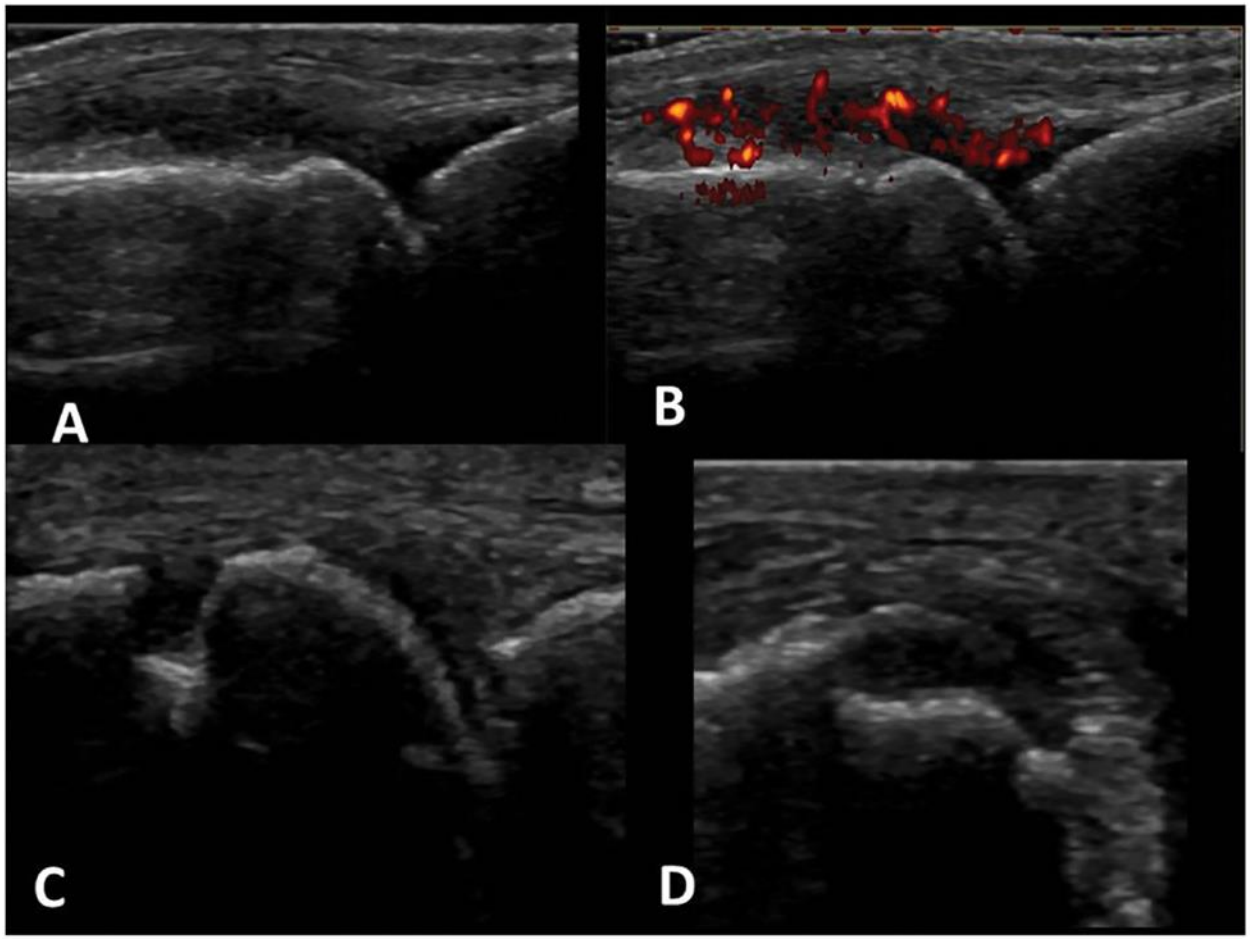
5.10.4 *Validation of BILAG A and B*

Ultrasound validated the distinction between BILAG-A and B MSK disease. All BILAG-A patients had moderate to severe PD synovitis compared with only 35% of BILAG-B ($P < 0.0001$).

5.10.5 *Erosions*

Ultrasound revealed erosive disease in non-rhupus SLE (Figure 5-3). The presence of erosions correlated with clinical synovitis (29% of MSK-BILAG-A vs. 4% of MSK-BILAG-C, $P = 0.0126$; 25% of MSK-SLEDAI = 4 vs. 5% of MSK-SLEDAI = 0, $P = 0.005$). Erosions tended to be mild and not affecting multiple joints.

Figure 5-3. Ultrasound image:



Erosion in SLE patient US synovitis and erosions detected in SLE patients (**A**): Grade 2 GS synovitis in fourth MCP joint, (**B**): grade 3 PD synovitis in fourth MCP joint, (**C**): Longitudinal view of an erosion in a second MCP joint, (**D**): Transverse view of the same erosion seen on (**C**). GS: grey scale.

5.10.6 Joint-by-joint agreement between clinical and ultrasound assessment

Overall agreement between clinical and ultrasound assessment on joint-by-joint analysis, as measured by Kappa and prevalence-adjusted-bias-adjusted Kappa, was reasonably good (table5.10.6). However, when analysing specific agreement for the presence or absence of synovitis there was considerable disagreement, indicating a degree of inaccuracy of clinical assessment in SLE against ultrasound as a gold standard. For the absence of synovitis, the agreement between clinical assessment and ultrasound appeared generally good across all joints assessed. However, this is because most joints were normal by both techniques. For the presence of synovitis, the agreement was poor. Therefore, there is no joint in which

ultrasound confirmed synovitis could be reliably detected using clinical assessment. Even in the joints with the best agreement (second and third PIP joints), there was only a ~50% chance that if ultrasound detected synovitis were present, it would be detected clinically.

Table 5-3. Joint by joint agreement between ultrasound and clinical assessment for synovitis as defined by swollen joints

Joint	US criterion	PEA	US<clinical	US>clinical	Sp(-ve)	Sp(+ve)	Kappa (95% CI)	PABAK
IP1	GS>0	82.0% (141/172)	1.2% (2/172)	16.9% (29/172)	89.8%(274/305)	20.5% (8/39)	0.16 (0.00, 0.31)	0.64
	GS>1	84.3% (145/172)	1.2% (2/172)	14.5% (25/172)	91.3% (282/309)	22.9% (8/35)	0.18 (0.01, 0.36)	0.69
	PD>0	90.1% (155/172)	1.7% (3/172)	8.1% (14/172)	94.7% (304/321)	26.1% (6/23)	0.22 (-0.02, 0.46)	0.80
	GS&PD>1	84.3% (145/172)	1.2% (2/172)	14.5% (25/172)	91.3% (282/309)	22.9% (8/35)	0.18 (-1.56, 1.93)	0.69
MCP1	GS>0	80.0% (140/175)	1.1% (2/175)	18.9% (33/175)	88.4% (266/301)	28.6% (14/49)	0.22 (-1.31, 1.75)	0.60
	GS>1	89.5% (154/172)	1.2% (2/172)	9.3% (16/172)	94.2% (294/312)	43.8% (14/32)	0.39 (0.17, 0.61)	0.79
	PD>0	94.8% (163/172)	1.7% (3/172)	3.5% (6/172)	97.2% (314/323)	57.1% (12/21)	0.54 (0.28, 0.81)	0.90
	GS&PD>1	89.5% (154/172)	1.2% (2/172)	9.3% (16/172)	94.2% (294/312)	43.8% (14/32)	0.39 (0.17, 0.61)	0.79
MCP2	GS>0	71.5% (123/172)	4.1% (7/172)	24.4% (42/172)	81.4% (214/263)	39.5% (32/81)	0.25 (0.11, 0.39)	0.43
	GS>1	80.2% (138/172)	7.0% (12/172)	12.8% (22/172)	88.2% (254/288)	39.3% (22/56)	0.28 (0.10, 0.46)	0.60
	PD>0	84.3% (145/172)	7.0% (12/172)	8.7% (15/172)	90.8% (268/295)	44.9% (22/49)	0.36 (-1.56, 2.28)	0.69
	GS&PD>1	80.2% (138/172)	7.0% (12/172)	12.8% (22/172)	88.2% (254/288)	39.3% (22/56)	0.28 (-1.52, 2.08)	0.60
MCP3	GS>0	61.0% (105/172)	3.5% (6/172)	35.5% (61/172)	74.3% (194/261)	19.3% (16/83)	0.07 (-0.04, 0.17)	0.22
	GS>1	82.0% (141/172)	4.1% (7/172)	14.0% (24/172)	89.6% (268/299)	31.1% (14/45)	0.22 (0.04, 0.41)	0.64
	PD>0	86.0% (148/172)	4.1% (7/172)	9.9% (17/172)	92.2% (282/306)	36.8% (14/38)	0.30 (0.09, 0.50)	0.72
	GS&PD>1	80.2% (138/172)	4.1% (7/172)	15.7% (27/172)	88.5% (262/296)	29.2% (14/48)	0.20 (0.03, 0.37)	0.60
MCP4	GS>0	62.8% (108/172)	1.2% (2/172)	36.0% (62/172)	76.6% (210/274)	8.6% (6/70)	0.03 (-0.67, 0.74)	0.26
	GS>1	82.0% (141/172)	1.2% (2/172)	16.9% (29/172)	89.9% (276/307)	16.2% (6/37)	0.12 (-1.35, 1.59)	0.64
	PD>0	90.1% (155/172)	1.2% (2/172)	8.7% (15/172)	94.7% (304/321)	26.1% (6/23)	0.23 (-0.01, 0.46)	0.80
	GS&PD>1	82.0% (141/172)	1.2% (2/172)	16.9% (29/172)	89.9% (276/307)	16.2% (6/37)	0.12 (-0.03, 0.26)	0.64

Joint	US criterion	PEA	US<clinical	US>clinical	Sp(-ve)	Sp(+ve)	Kappa (95% CI)	PABAK
MCP5	GS>0	71.5% (123/172)	0.6% (1/172)	27.9% (48/172)	82.8% (236/285)	16.9% (10/59)	0.11 (0.01, 0.22)	0.43
	GS>1	85.5% (147/172)	0.6% (1/172)	14.0% (24/172)	91.9% (284/309)	28.6% (10/35)	0.24 (0.06, 0.43)	0.71
	PD>0	92.4% (159/172)	0.6% (1/172)	7.0% (12/172)	96.0% (308/321)	43.5% (10/23)	0.40 (0.15, 0.66)	0.85
	GS&PD>1	85.5% (147/172)	0.6% (1/172)	14.0% (24/172)	91.9% (284/309)	28.6% (10/35)	0.24 (0.06, 0.43)	0.71
MTP1	GS>0	47.4% (55/116)	0.9% (1/116)	51.7% (60/116)	63.9% (108/169)	3.2% (2/63)	Not calculated	-0.05
	GS>1	71.6% (83/116)	0.9% (1/116)	27.6% (32/116)	83.2% (164/197)	5.7% (2/35)	0.03 (-0.06, 0.11)	0.43
	PD>0	92.2% (107/116)	1.7% (2/116)	6.0% (7/116)	96.0% (214/223)	0.0% (0/9)	Not calculated	0.84
	GS&PD>1	72.4% (84/116)	0.9% (1/116)	26.7% (31/116)	83.8% (166/198)	5.9% (2/34)	0.03 (-0.06, 0.12)	0.45
MTP2	GS>0	71.6% (83/116)	0.0% (0/116)	28.4% (33/116)	83.1% (162/195)	10.8% (4/37)	0.08 (-0.03, 0.18)	0.43
	GS>1	85.3% (99/116)	0.0% (0/116)	14.7% (17/116)	91.9% (194/211)	19.0% (4/21)	0.16 (-0.04, 0.37)	0.71
	PD>0	97.4% (113/116)	1.7% (2/116)	0.9% (1/116)	98.7% (226/229)	0.0% (0/3)	Not calculated	0.95
	GS&PD>1	85.3% (99/116)	0.0% (0/116)	14.7% (17/116)	91.9% (194/211)	19.0% (4/21)	0.16 (-0.04, 0.37)	0.71
MTP3	GS>0	77.8% (91/117)	0.0% (0/117)	22.2% (26/117)	87.1% (176/202)	18.8% (6/32)	0.15 (0.00, 0.30)	0.56
	GS>1	88.0% (103/117)	0.0% (0/117)	12.0% (14/117)	93.5% (200/214)	30.0% (6/20)	0.27 (0.02, 0.51)	0.76
	PD>1	96.6% (113/117)	1.7% (2/117)	1.7% (2/117)	98.2% (224/228)	33.3% (2/6)	0.32 (-0.18, 0.81)	0.93
	GS&PD>1	88.0% (103/117)	0.0% (0/117)	12.0% (14/117)	93.5% (200/214)	30.0% (6/20)	0.27 (0.02, 0.51)	0.76
MTP4	GS>0	83.6% (97/116)	0.9% (1/116)	15.5% (18/116)	91.0% (192/211)	9.5% (2/21)	0.07 (-0.09, 0.22)	0.67
	GS>1	91.4% (106/116)	1.7% (2/116)	6.9% (8/116)	95.5% (212/222)	0.0% (0/10)	Not calculated	0.83
	PD>1	98.3% (114/116)	1.7% (2/116)	0.0% (0/116)	99.1% (228/230)	0.0% (0/2)	Not calculated	0.97
	GS&PD>1	91.4% (106/116)	1.7% (2/116)	6.9% (8/116)	95.5% (212/222)	0.0% (0/10)	Not calculated	0.83

Joint	US criterion	PEA	US<clinical	US>clinical	Sp(-ve)	Sp(+ve)	Kappa (95% CI)	PABAK
MTP5	GS>0	90.5% (105/116)	0.0% (0/116)	9.5% (11/116)	95.0% (210/221)	0.0% (0/11)	Not calculated	0.81
	GS>1	98.3% (114/116)	0.0% (0/116)	1.7% (2/116)	99.1% (228/230)	0.0% (0/2)	Not calculated	0.97
	PD>0	99.1% (115/116)	0.0% (0/116)	0.9% (1/116)	99.6% (230/231)	0.0% (0/1)	Not calculated	0.98
	GS&PD>1	98.3% (114/116)	0.0% (0/116)	1.7% (2/116)	99.% (228/230)	0.0% (0/2)	Not calculated	0.97
PIP2	GS>0	80.8% (139/172)	2.9% (5/172)	16.3% (28/172)	88.3% (248/281)	47.6% (30/63)	0.38 (-1.19, 1.95)	0.62
	GS>1	85.5% (147/172)	3.5% (6/172)	11.0% (19/172)	91.4% (266/291)	52.8% (28/53)	0.45 (0.27, 0.63)	0.71
	PD>0	87.2% (150/172)	6.4% (11/172)	6.4% (11/172)	92.8% (282/304)	45.0% (18/40)	0.38 (0.17, 0.59)	0.74
	GS&PD>1	85.5% (147/172)	3.5% (6/172)	11.0% (19/172)	91.4% (266/291)	52.8% (28/53)	0.45 (0.27, 0.63)	0.71
PIP3	GS>0	76.7% (132/172)	1.7% (3/172)	21.5% (37/172)	85.1% (228/268)	47.4% (36/76)	0.36 (0.22, 0.50)	0.53
	GS>1	82.6% (142/172)	2.9% (5/172)	14.5% (25/172)	89.4% (252/282)	51.6% (32/62)	0.42 (0.26, 0.59)	0.65
	PD>0	86.6% (149/172)	4.7% (8/172)	8.7% (15/172)	92.2% (272/295)	53.1% (26/49)	0.45 (-1.41, 2.32)	0.73
	GS&PD>1	82.6% (142/172)	2.9% (5/172)	14.5% (25/172)	89.4% (252/282)	51.6% (32/62)	0.42 (0.26, 0.59)	0.65
PIP4	GS>0	79.1% (136/172)	2.3% (4/172)	18.6% (32/172)	87.8% (258/294)	28.0% (14/50)	0.20 (0.04, 0.36)	0.58
	GS>1	86.6% (149/172)	2.3% (4/172)	11.0% (19/172)	92.5% (284/307)	37.8% (14/37)	0.32 (0.11, 0.52)	0.73
	PD>0	87.2% (150/172)	3.5% (6/172)	9.3% (16/172)	92.9% (290/312)	31.3% (10/32)	0.25 (0.03, 0.47)	0.74
	GS&PD>1	86.6% (149/172)	2.3% (4/172)	11.0% (19/172)	92.5% (284/307)	37.8% (14/37)	0.32 (0.11, 0.52)	0.73
PIP5	GS>0	82.6% (142/172)	1.7% (3/172)	15.7% (27/172)	90.2% (276/306)	21.1% (8/38)	0.15 (0.00, .031)	0.65
	GS>1	89.5% (154/172)	2.3% (4/172)	8.1% (14/172)	94.4% (302/320)	25.0% (6/24)	0.20 (-0.03, 0.44)	0.79
	PD>0	90.7% (156/172)	2.9% (5/172)	6.4% (11/172)	95.1% (308/324)	20.0% (4/20)	0.16 (-0.09, 0.40)	0.81
	GS&PD>1	89.5% (154/172)	2.3% (4/172)	8.1% (14/172)	94.4% (302/320)	25.0% (6/24)	0.20 (-0.03, 0.44)	0.79

Joint	US criterion	PEA	US<clinical	US>clinical	Sp(-ve)	Sp(+ve)	Kappa (95% CI)	PABAK
Wrist	GS>0	57.6% (99/172)	2.3% (4/172)	40.1% (69/172)	70.7% (176/249)	23.2% (22/95)	0.10 (0.01, 0.19)	0.15
	GS>1	79.7% (137/172)	3.5% (6/172)	16.9% (29/172)	88.0% (256/291)	34.0% (18/53)	0.25 (0.08, 0.41)	0.59
	PD>0	80.2% (138/172)	5.2% (9/172)	14.5% (25/172)	88.6% (264/298)	26.1% (12/46)	0.16 (-0.01, 0.34)	0.60
	GS&PD>0	79.1% (136/172)	3.5% (6/172)	17.4% (30/172)	87.6% (254/290)	33.3% (18/54)	0.24 (0.07, 0.40)	0.58

PEA: Percentage exact agreement; Sp(+ve): proportions of category-specific positive agreement(clinical +ve, ultrasound +ve); Sp(-ve): proportions of category-specific negative agreement(clinical –ve, ultrasound –ve); PABAK: Prevalence-adjusted bias-adjusted kappa.

5.10.7 *Subclinical synovitis is associated with objective and symptomatic evidence of inflammation*

In the subclinical synovitis group, substantial numbers (30% of MSK-BILAG=C and 26% of MSK-SLEDAI = 0) had moderate-severe power Doppler (a severe and specific abnormality). Tenosynovitis was common in the subclinical synovitis group, affecting just under half of patients.

To analyse the clinical significance of subclinical synovitis, I selected patients without joint swelling. Because most abnormities were detected in the hands and wrists, and to compare with a 28-joint count and DAS28, I analysed ultrasound data in the hands and wrists only. I analysed physician VAS, and IgG and ESR, which were associated with clinical synovitis in the whole cohort. These variables were compared according to the presence or absence of ultrasound synovitis, as well as the main categories of abnormality: GS, PD and tenosynovitis (Table 5-4). Subclinical synovitis was associated with serological evidence of disease activity: IgG titre was significantly higher in the presence of overall synovitis (P = 0.002), GS synovitis (P = 0.003) and PD/tenosynovitis (P = 0.045). Patients with tenosynovitis or PD synovitis also had higher tender joint count (P = 0.024) and showed some evidence of higher physician VAS (P = 0.056), and DAS28-ESR (P = 0.061). Although the difference in DAS28 was not significant at alpha = 0.05 the large descriptive difference between patients with/without PD/tenosynovitis (median 4.82 vs. 3.09) warrants investigation in a larger cohort.

Table 5-4. Clinical and serological characteristics of symptomatic patients without joint swelling according to ultrasound status:

	Overall US Abnormality			Grey Scale			Tenosynovitis or PD		
	No (n=36)	**Yes** (n=17)	***P***	**No** (n=38)	**Yes** (n=15)	***P***	**Both –** (n=43)	**Either +** (n=10)	***P***
Physician VAS	5 (0,16)	10 (0,25)	0.354	5 (0,17)	7 (0,26)	0.668	5 (0,16)	18 (6,26)	0.056
Tender Joint Count	1.5 (0,8)	2 (1,9)	0.310	2 (0,8)	2 (1,10)	0.511	1 (0,7)	7 (3,14)	0.024
IgG	10.9 (9.0,14.0)	14.8 (13.9,16.5)	0.002	11.2 (9.0,14.4)	14.8 (13.6,16.5)	0.003	11.5 (9.3,14.8)	16.2 (13.3,16.5)	0.045
ESR	11 (6-33)	20 (11,34)	0.106	11 (6,33)	20 (11,34)	0.106	13 (8,29)	16 (11,88)	0.417
DAS28-ESR	3.25 (1.48,4.41)	3.43 (2.52,4.96)	0.293	3.25 (1.48,4.41)	3.43 (2.52,4.96)	0.293	3.09 (1.69,4.14)	4.82 (2.85,5.31)	0.061

Analysis of patients with no joint swelling (MSK-SLEDAI=0). Values are median (IQR). Joints assessed by Ultrasound in this analysis were hands and wrists. Clinical assessment was 28 joint set. Tenosynovitis GS1 was considered abnormal

5.11 Discussion:

In this study, I reported results from a large cohort of patients. I demonstrated that more than 25% of SLE patients with inflammatory musculoskeletal symptoms had proven synovitis, which is associated with worse clinical and serological assessments but not detected by validated disease activity tools. The importance of this result is treating SLE patients with common manifestation, as well as for conducting and interpretation of clinical trials.

According to the EULAR taskforce recommendation that in order to achieve the best long-term outcomes, SLE patients should be treated to a target of low disease activity measured using validated instruments while minimum glucocorticoid exposure [24]. BILAG and SLEDAI are the instruments most widely used. These results show the limitation of directing treatment according to these instrument in musculoskeletal SLE and their likely consequences. In patients with ongoing inflammatory symptoms but not meeting SLEDAI-MSK criteria or BILAG A/B, therapy might not be escalated or changed despite definite synovitis. Despite the current therapy Quality of life and work disability are impaired in SLE, and musculoskeletal symptoms are one of the strongest determinants of this [25, 26]. Failure to escalate therapy is therefore likely to result in serious adverse long-term outcomes.

Conversely, the treat to target recommendation is focusing on the need to minimize glucocorticoid exposure. This is because there is a dose-related association between glucocorticoid exposure and accrual of damage [27, 28]. I showed that imaging can identify 35% of patients who present with seemingly inflammatory symptoms (attributed to SLE activity and rated BILAG C) in whom there was no objective evidence of synovitis and glucocorticoids would therefore not be the appropriate treatment. Better tools to assess musculoskeletal disease activity would, therefore, help physicians to reduce prescribing of glucocorticoids.

Treat-to-target regimens have been shown to be effective in RA using clinical criteria, but not in more recent studies using ultrasound target [29, 30]. However, there are significant

differences between these diseases and protocols. In RA all patients have joint swelling at some point (to meet criteria) while in SLE this is not essential for the diagnosis. Also, in RA the DAS28 captures any tender joint regardless of aetiology, as well as patient VAS. Whereas in SLE, only symptoms deemed to represent SLE disease activity by a physician are rated. Therefore, in RA the DAS28 maximizes sensitivity over specificity, while in SLE there is a greater emphasis on specificity for true joint inflammation, which has important implications in comparison to ultrasound for treating-to-target.

Identifying active disease is essential to produce reliable clinical trial results. Placebo response rates in SLE trials are notably high, sometimes >40% for SRI-4 in recent phase II and III trials [31, 32]. Although I found that joint swelling is usually indicative of ultrasound-proven synovitis, this is not always required for entry into clinical trials; the SLEDAI allows scoring for arthritis based on warmth, tenderness or swelling reported by the patient in the past 30 days rather than measured on clinical examination. These criteria have not been independently validated. Further work is required to determine whether superior clinical instruments could be defined using ultrasound as a gold standard.

Several previous studies assessed musculoskeletal ultrasound in SLE, but we identified limitations and inconsistencies that the present study was designed to resolve [14, 33–41]. Since our group systematic review, one additional study has reported clinical and ultrasound findings in a large cohort of patients [42]. There were unusually high rates of ultrasound abnormality, e.g., in 85% of asymptomatic patients, with PD in 37% of asymptomatic patients. The reason for these unusually high rates is not clear (although some rhupus patients were included). However, because so few patients had normal ultrasound it was not possible to address the central objective of my study in their dataset: to describe the prevalence and clinical associations of ultrasound synovitis in patients without joint swelling compared with patients with swelling, and those with active symptoms but normal ultrasound. Strengths of my study were the recruitment of consecutive patients to allow estimates of prevalence,

exclusion of rhupus, control for NSAID and glucocorticoid use and reporting OMERACT grades of ultrasound abnormality. There are a number of choices of OMERACT grades of abnormality to be reported. These may vary by clinical site – for example, GS change is commonly seen in the feet in healthy individuals. I chose to use GS > 2 or PD > 1 based on OMERACT definitions and data in other inflammatory arthritides and provide the first analysis of the clinical significance of these definitions against symptoms and serology in SLE in our paper, as well as a joint-by-joint comparison with clinical evaluation.

This study has a number of limitations. Even in this larger patient group, it is difficult to reliably assess the symptomatic impact of subclinical synovitis and longitudinal follow-up is required. Confirmation that ultrasound positive patients respond better to therapy is needed to confirm that ultrasound synovitis should be an indication for immunosuppressive therapy. Longitudinal data after treatment is also needed to determine relative responsiveness of ultrasound and BILAG/SLEDAI to determine whether existing instruments are underestimating the effectiveness of therapy in clinical trials.

5.12 Conclusion

The results demonstrate the limitations of the current classification of active musculoskeletal SLE based on joint swelling, BILAG and SLEDAI and that a new classification of proven musculoskeletal inflammation may allow improvement in outcomes of immunosuppressive therapy.

5.13 Key messages

1-More than a quarter of SLE patients with arthralgia had objective inflammation on ultrasound not detected by the available clinical instruments.

2-The BILAG and SLEDAI instruments had high specificity but low sensitivity for ultrasound-confirmed synovitis.

3-Ultrasound-only inflammation is associated with worse clinical symptoms and serology in comparison with patients with normal scan.

Chapter 6: Pilot Longitudinal Study: Responsiveness of clinical and ultrasound outcome measures in musculoskeletal systemic lupus erythematosus:

6.1 Introduction

Inflammatory musculoskeletal features are common in SLE, being the first presenting symptom in around 50% of cases and affecting up to 95% of patients at some time [124, 158]. Joint pain in SLE has a significant impact on quality of life and results in loss of function [7, 36, 400]. Accordingly, musculoskeletal disease is a common reason for inclusion into clinical trials.

Recent phase III trials of many putative treatments in non-renal SLE have been negative (with the exception of belimumab [401]). This has led to questions over the most appropriate outcome measures to use in SLE trials. Also, in clinical practice, it is equally important to differentiate patients with good or incomplete responses to therapy for treat-to-target approaches and to minimize glucocorticoid use [402].

While non-renal SLE trials included many different types of organ involvement, musculoskeletal disease was most common. For example, in the pooled data from the study of belimumab in subjects with SLE, BLISS52 and BLISS76 trials, 1008/1684 (60%) patients had musculoskeletal (MSK)-BILAG A or B at baseline; 991/1684 (59%) had mucocutaneous BILAG A or B; and 272/1684 (16%) had haematology A or B; with lower percentages for other organ systems. In the phase III Efficacy and safety of subcutaneous tabalumab in patients with SLE (ILLUMINATE) study, at baseline, 81% of patients had musculoskeletal activity on the SLEDAI [395]

In SLE, outcome measures must account for disease activity in many different organs. For this reason, less detail is included for each organ compared with more organ-specific instruments such as the 28 joint count used in RA. The SLEDAI and BILAG, and composite

endpoints derived from them such as the SLE responder index 4 (SRI-4) and BILAG-based composite SLE assessment, are commonly used in trials.

For musculoskeletal involvement, the SLEDAI-2K [219] is binary, scoring four points for tenderness with swelling, effusion, warmth or erythema in two or more joints in the past 30 days, and none for lesser degrees of arthritis. This scoring means that patients with a high level of disease activity at baseline who have a substantial improvement may be considered non-responders. The BILAG-2004 index[403] is semi-quantitative with four grades for each active organ system assessed. For the musculoskeletal domain, BILAG A (the highest score) requires observed active synovitis in more than two joints with marked loss of functional range of movements. BILAG B is scored for tendonitis/tenosynovitis or active synovitis in more than one joint (observed or through history) with some loss of functional range of movement (or improving BILAG A disease). BILAG C is scored for inflammatory pain (e.g. with morning stiffness) without synovitis (or improving BILAG B disease). Pain without inflammatory symptoms (e.g. pain that clinically appears to be because of osteoarthritis) is scored as BILAG D or E, as are patients with previous joint inflammation but no current symptoms. Assigning these grades is dependent on the skill of the assessor, and in both these indices, the assessor must only score symptoms that are deemed to be due to active SLE rather than other pathologies, which is known to be a difficult distinction for arthralgia in many inflammatory arthritides.

Joint counts and visual analogue scales (VAS) have also been used in many SLE trials, but with limited independent validation [386]. Musculoskeletal ultrasound provides an objective measure of synovitis that has already been shown to have face and construct validity in SLE [308]. In my cross-sectional study(Chapter 5:) I showed that the BILAG and SLEDAI are specific but not sensitive for the detection of synovitis that is ultrasound confirmed and associated with worse symptoms and serological abnormality[404]. These various instruments have never been compared longitudinally.

6.2 Objective:

The objective of this study was therefore to compare the internal responsiveness of a range of clinical outcome measures and ultrasound in SLE patients receiving a therapy of known efficacy (glucocorticoids).

6.3 Patients and methods:

A prospective pilot study was conducted in 20 Patients fulfilling the Systemic Lupus International Collaborating Clinics (SLICC) 2012 diagnostic criteria for SLE with inflammatory musculoskeletal symptoms [19] were recruited in Leeds if they had been prescribed 120mg intramuscular methylprednisolone acetate(Depo-Medrone) for active musculoskeletal disease that day as part of their routine care. Other eligibility criteria included: patients should be on stable doses of NSAID, DMARDs and glucocorticoids (up to prednisolone ≤5mg/day or equivalent) for at least six weeks. Anti-cyclic citrullinated peptide Antibody (CCP) positive patients and those with improving disease were excluded. Ultrasound and clinical assessment were performed on the day of intramuscular glucocorticoid treatment and repeated after 2 and 4 weeks to evaluate responsiveness. I did not withdraw patients based on their baseline clinical and ultrasound assessment.

6.4 Ethical approval:

The study was approved by the local ethics committee and informed written consent was obtained from all patients (Leeds East Research Ethics Committee 10/H1306/88).

6.5 Clinical and laboratory assessment:

Clinical assessments were performed by trained rheumatologists who were blinded to the ultrasound assessment. SLE activity was assessed using BILAG-2004 [169], SLEDAI-2K 30 days[388] Joint disease was assessed using 28 tender and swollen joint counts, painful joint count, physician musculoskeletal visual analogue score (VAS), patient's musculoskeletal disease activity VAS and minutes of early morning stiffness. BILAG-2004 numerical scores

were calculated using the formula A=12, B=8, C=1, D/E=0[170]. The BILAG-2004 is assessed over the previous 28 days. The SLEDAI-2K and SRI-4 have been validated measuring symptoms over the previous 10 or 30 days[405, 406]. Response to Depo-Medrone is typically seen within a few days. For the purposes of this study, I allowed a 5-day window for follow up study visits and patients who reported rapid improvement in symptoms within a few days of the injection and for the majority of the period since the baseline visit to have a 4-week response at the last assessment.

Patients were tested at baseline for routine inflammatory and serological markers. SLE Responder Index (SRI-4) was calculated as previously described[3]. SRI-4 response criteria were met if the patient had: at least a 4-point reduction in the SLEDAI-2K, no worsening in physician VAS, no worsening in BILAG.

6.6 Ultrasound assessment

Ultrasound (GS and PD) was performed using high-resolution US machine (HRUS). General Electric (GE) Logiq E9 HRUS with multi-linear 6-15 MHz transducer was used. For the details of the ultrasound examination, please see 4.1.

6.7 Statistical analysis

Clinical characteristics (demographics, clinical assessments, therapies and immunological parameters) and ultrasound features were summarized for each group using percentages of patients or median and interquartile range as appropriate.

Different methods have been used to calculate effect sizes to measure internal responsiveness. Standardised response means may be used for parametric variables. The candidate outcome measures in this study included parametric, ordinal and categorical variables. Therefore I used effect sizes calculated from a paired non-parametric test instead of paired t-tests usually used to calculate effect size statistics[407]. Change in continuous variables was assessed using Wilcoxon Signed Ranks test. Effect size was calculated using standardized test statistic, Z, using the formula r=Z/sqrt (n1+n2). Effect sizes were judged

using Cohen's Criteria as large (>-0.5), medium (>-0.3) or small (>-0.1)[408].

6.8 Results

6.8.1 *Baseline characteristics*

All of the 20 patients were female and ANA positive. Mean (SD) age was 49.7 (14.1) and mean (SD) disease duration 85 months (22). There were 11/20 (55%) were receiving NSAID (non-steroid anti-inflammatory drug) therapy. Fourteen patients were on a stable dose of hydroxychloroquine, of whom three were also on a stable dose of methotrexate or mycophenolate and one was on epratuzumab. Three patients received methotrexate or mycophenolate without hydroxychloroquine. Three patients were not on hydroxychloroquine or other oral immunosuppressant medications. Three patients received a stable dose of prednisolone ≤5mg/day. Fifteen (15/20) patients had clinical joint swelling at baseline. The others all had either US synovitis (GS in 18/20, PD in 17/20) or >60 minutes of EMS, or new activity in other organ systems coincident with the onset of joint pain.

Table 6-1: Baseline characteristics

	All patients N= 20
Age(years) Mean(SD)	49.7 (14.1)
Disease duration(months) Mean(SD)	85 (22)
Therapy	
NSAID n/N %	11/20 (55%)
Hydroxychloroquine n/N%	14/20 (70%)
Methotrexate n/N%	3/20 (15%)
Prednisolone n/N%	3/20 (15%)
Clinical assessment	
Swollen joint%	15/20 (75%)
Ultrasound abnormalities	
Grey scale	18/20 (90%)
Power Doppler	17/20 (85%)

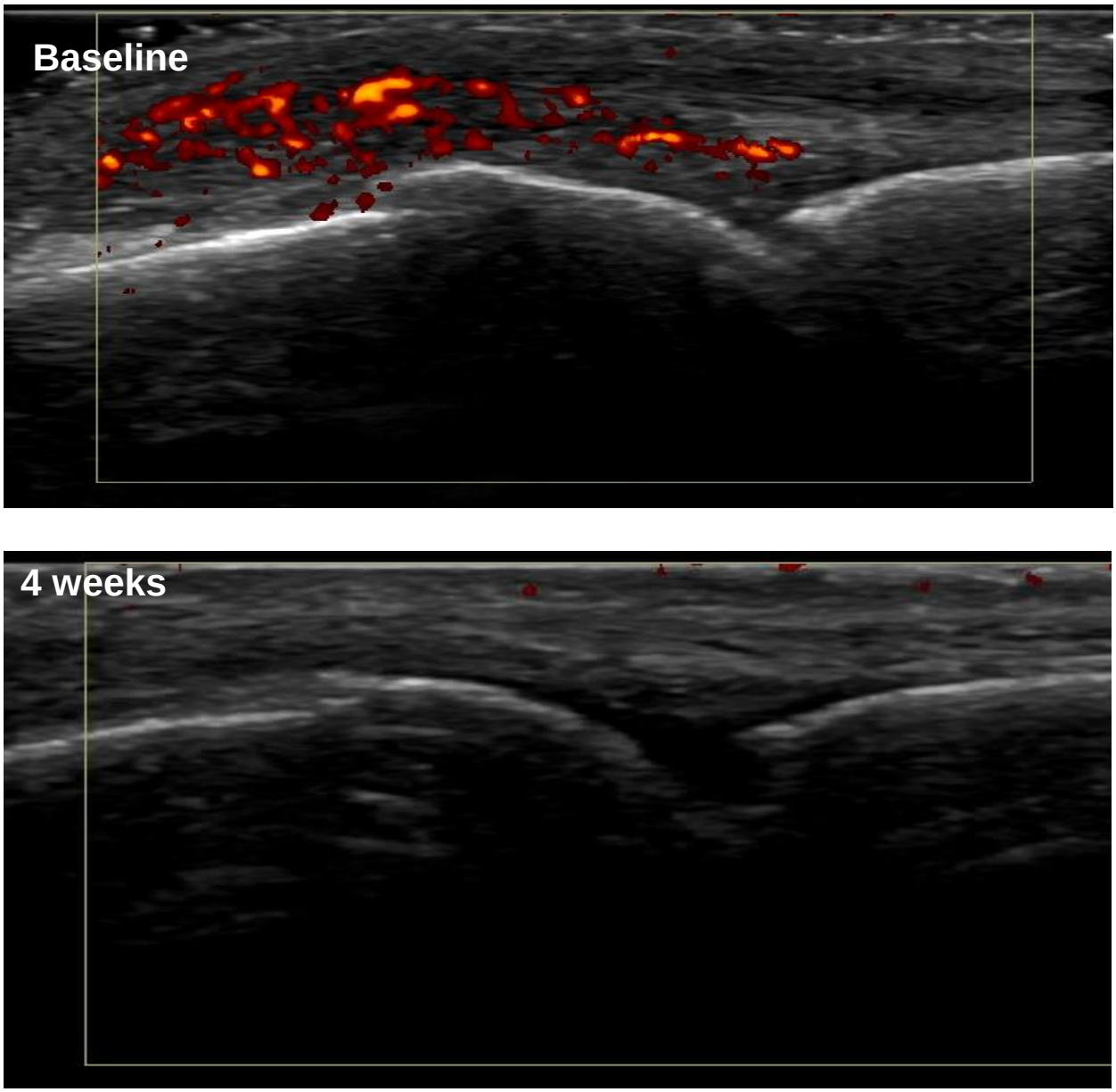
6.8.2 Week 2, 4 Changes in outcome measures

At four weeks there was a substantive and significant improvement in all clinical and ultrasound parameters measured (all $p<0.025$, Table 6-2). However, 65% of patients still had symptoms with BILAG A-C. Eighty percent (16/20) of the patients had improvement by at least one MSK-BILAG grade, but only 7/20 had improvement in the musculoskeletal SLEDAI component. Residual symptoms were confirmed by tender and symptomatic joint count, morning stiffness, patient and physician VAS. On 4-week ultrasound, there was a large reduction in PD. PD was present in nine patients at four weeks, but with a total score of <2 in

8 of these (Figure 6-1). GS scores were significantly reduced but higher than PD post-treatment, being present at ≥2 in 13/20 patients. Changes in these parameters at 2 weeks were more variable. Tender and swollen joint counts and EMS minutes had numerically, but not statistically significantly improved. Visual analogue scales showed a partial but significant improvement. Ultrasound parameters had all significantly improved at 2 weeks, although to lesser degree than at 4 weeks. Table 6-3 demonstrates effect sizes, ordered according to magnitude. At both 2 and 4 weeks, physician VAS had the largest effect size, although it must be noted that this assessment was not blinded to time point and may be more susceptible to observer bias than the other variables. Other than physician VAS, at 2 weeks only changes in ultrasound showed large effect sizes. Changes in clinical variables were only small-medium.

At week 4, effect sizes remained large for ultrasound parameters and physician VAS. They were medium for other clinical variables (joint counts, EMS, patient VAS). Effect sizes for musculoskeletal components of BILAG and SLEDAI differed: the effect for MSK-BILAG was of a similar magnitude to ultrasound. Although the MSK-SLEDAI significantly improved, its effect size was substantially smaller than for BILAG, ultrasound and physician VAS.

Figure 6-1, Ultrasound images showing changes in PD between baseline and week4:



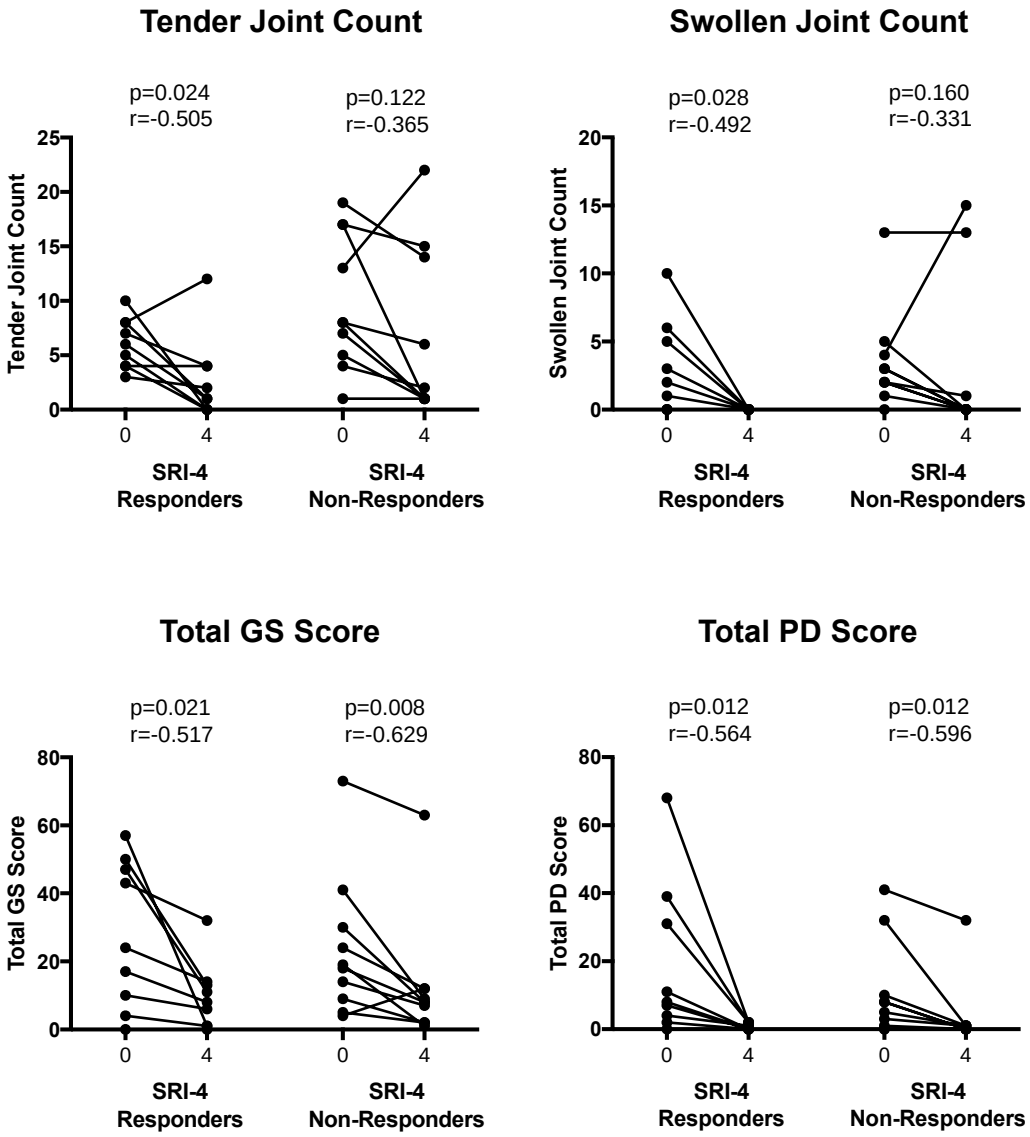
US images of MCP joint in an SLE patient at baseline and 4 weeks. Baseline image shows grade 3 power Doppler, which has completely resolved at 4 weeks.

6.8.3 *Comparison of SLEDAI responders and non-responders*

The 19 patients with MSK-SLEDAI score of at least four points at baseline were grouped into SRI-4 responders (n=9) and SRI-4 non-responders (n=10). SRI-4 and change in MSK-SLEDAI were generally equivalent in this patient group. All SRI-4 responders also had improvement in the musculoskeletal component of the SLEDAI except for one who improved

in other organ domains and had a mixed response in musculoskeletal variables (Figure 6-2). All SRI-4 non-responders did not have improvement in the musculoskeletal component of the SLEDAI. After that, I compared changes in tender and swollen joint counts, ultrasound greyscale and PD in each of these groups. For tender and swollen joint counts, there were large effect sizes in SRI-4 responders (r=-0.505 and -0.492 respectively and p=0.024 and 0.028 respectively) and a medium effect sizes in SRI-4 Non-responders (r=-0.365 and -0.331 and p=0.122 and 0.160). For ultrasound, large effect sizes for improvements in both GS and PD were observed in both SRI-4 responders (r=-0.517 and -0.564 and p=0.021 and 0.021) and SRI-4 non-responders (r=-0.629 and -0.596 and p=0.008 and 0.012).

Figure 6-2. Change in joint counts and ultrasound and SRI-4 response:



Patients who had a MSK-SLEDAI score of 4 points at baseline were grouped according to whether they met the SRI-4 response criterion at 4-week follow up. P-values show the results of a Wilcoxon matched pairs test within each group and effect size r

Table 6-2 . Summaries of clinical and ultrasound assessments at weeks 0, 2 & 4:

Outcome Measure	Week 0	Week 2	Week 4	Change Week 2	Change Week 4
BILAG-MSK n (%) **A** **B** **C** **D**	 7/20 (35) 8/20 (40) 5/20 (25)	N/A	 1/20 (5) 2/20 (10) 9/20 (45) 7/20 (35)	N/A	 Improved 16/20 (80%) Same 4/20 (20%) Worse 0/20 (0%)
BILAG-MSK **(A=12, B=8, C=1, D=0)**	8 (3,12)	N/A	1 (0,1)	N/A	-7 (-8, -1)
SLEDAI arthritis present n (%)	19/20 (95)	N/A	10/20 (50)	N/A	Improved 7/20 (35%) Same 13/20 (65%)
SLEDAI arthritis	4 (4, 4)	N/A	2 (0, 4)	N/A	0 (-4, 0)
TJC (0-28)	8 (4, 12)	4 (1,14)	2 (1, 11)	-3 (-4, 3)	-4 (-6, -1)
SJC (0-28)	2 (0, 5)	0 (0,1)	0 (0-0)	-1 (-3, 0)	-2 (-3, 0)
Symptomatic joint count	15 (6, 22)	2 (0,13)	4 (1,15)	-7 (-19, 0)	-6 (-14, -1)
EMS (minutes)	25 (0, 60)	5 (0, 45)	3 (0, 41)	0 (-21, 0)	0 (-24, 0)
Patient VAS (mm)	57 (30, 79)	30 (9, 40)	33 (8, 49)	-23 (-29, -10)	-22 (-52, 2)
Physician VAS (mm)	55 (35, 68)	23 (5, 50)	15 (5, 35)	-24 (-45, -15)	-31 (-45, -15)
US - total PD	8 (2, 26)	1 (0, 6)	1 (0, 1)	-8 (-27, -2)	-8 (-10, -2)
US - total GS	19 (9, 43)	13 (5, 24)	8 (2, 13)	-12 (-23, -4)	-10 (-21, -3)
Joints with US synovitis	5.5 (1, 9)	3 (1, 8)	1 (0, 4)	-7 (-10, -3)	-5 (-12, -2)

All values presented are median (IQR) unless otherwise stated. TJC = tender joint count in 28 joints, SJC = swollen joint count in 28 joints, Symptomatic joint count = number of joints indicated as painful or stiff by patients on a graphical questionnaire. EMS = early morning stiffness, PD = total US power Doppler score, GS = total US greyscale score. Joints with US synovitis = number of joints scoring either GS>1 or PD>0.

Table 6-3. Effect size for change at 2 and 4 weeks according to magnitude

Week 0 – Week 2					
Outcome measure	**No. pairs**	**P**	**Z**	**Effect size**	**Cohen Criteria**
Physician VAS	16	0.001	-3.409	-0.603	Large
Grey Scale Score	16	0.002	-3.13	-0.571	Large
No. Joints with US Synovitis	16	0.011	-3.160	-0.559	Large
PD Score	16	0.002	-3.099	-0.548	Large
Symptomatic Joint Count	10	0.047	-1.988	-0.445	Medium
Patient VAS	16	0.016	-2.409	-0.426	Medium
EMS minutes	16	0.046	-1.997	-0.353	Medium
Swollen Joint Count	16	0.059	-1.889	-0.334	Medium
Tender Joint Count	15	0.274	-1.093	-0.200	Small
Week 0 – Week 4					
Outcome measure	**No. pairs**	**P**	**Z**	**Effect size, r**	**Cohen Criteria**
Physician VAS	20	<0.001	-3.388	-0.593	Large
MSK BILAG Numeric	20	0.008	-3.643	-0.576	Large
PD Score	20	<0.001	-3.627	-0.573	Large
No. Joints with US Synovitis	20	0.001	-3.627	-0.573	Large
Grey Scale Score	20	<0.001	-3.503	-0.554	Large
Symptomatic Joint Count	14	0.010	-2.576	-0.487	Medium
MSK-SLEDAI Score	20	0.003	-3.000	-0.474	Medium
Tender Joint Count	20	0.007	-2.683	-0.424	Medium
EMS minutes	20	0.012	-2.527	-0.400	Medium
Swollen Joint Count	20	0.007	-2.425	-0.383	Medium
Patient VAS	20	0.020	-2.331	-0.369	Medium

MSK BILAG Numeric calculated using A=12, B=8, C=1, D=0. MSK-SLEDAI Score calculated using arthritis present in previous 30 days = 4, arthritis absent = 0. P values are results of Wilcoxon signed ranks test, Z = standardized test statistic, effect size r calculated as r=Z/sqrt

Table 6-4SRI-4 response and musculoskeletal variables

Total SLEDAI Week 0	Total SLEDAI Week 4	Reduction in SLEDAI 0-4 Weeks	Four point reduction in SLEDAI	Reduction in physician VAS 0-4 Weeks (0-100mm)	BILAG Worsening?	SRI-4 met?	MSK SLEDAI Week 0	MSK SLEDAI Week 4	% Reduction TJC	% Redcution SJC	% Reduction GS	% Reduction PD
2	0	2	N/A*	9	No	N/A	0	0	12	0	6	-89
5	1	4	Yes	33	No	Yes	4	0	-50	100	-42	-75
4	0	4	Yes	65	No	Yes	4	0	100	100	-98	-94
6	2	4	Yes	16	No	Yes	4	0	83	0	-53	-100
4	0	4	Yes	15	No	Yes	4	0	43	0	-40	-100
6	2	4	Yes	80	No	Yes	4	0	100	100	-74	-97
8	2	6	Yes	30	No	Yes	4	0	100	100	-26	-100
8	4	4	Yes	30	No	Yes	4	0	0	100	-77	-95
7	3	4	Yes	4	No	Yes	4	0	88	100	-75	-100
6	2	4	Yes	28	No	Yes	4	0	33	0	0	0
9	5	4	Yes	38	No	Yes	4	4	88	0	200	0
10	18	-8	No	-15	Yes	No	4	4	25	100	50	0
8	8	0	No	32	No	No	4	4	12	50	50	100
8	8	0	No	45	No	No	4	4	0	100	95	67

Total SLEDAI Week 0	Total SLEDAI Week 4	Reduction in SLEDAI 0-4 Weeks	Four point reduction in SLEDAI	Reduction in physician VAS 0-4 Weeks (0-100mm)	BILAG Worsening?	SRI-4 met?	MSK SLEDAI Week 0	MSK SLEDAI Week 4	% Reduction TJC	% Redcution SJC	% Reduction GS	% Reduction PD
6	6	0	No	35	No	No	4	4	-69	100	73	90
6	4	2	No	50	No	No	4	4	50	100	78	97
8	8	0	No	5	No	No	4	4	26	0	14	22
17	22	-5	No	48	Yes	No	4	4	80	-275	56	100
6	6	0	No	29	No	No	4	4	94	100	78	80
4	4	0	No	45	No	No	4	4	86	100	60	100

GS= total US greyscale score, PD = total US power Doppler score TJC = tender joint count in 28 joints, SJC = swollen joint count in 28 joints

6.9 Discussion

In this study, I compared the internal responsiveness of clinical outcome measures and ultrasound in patients with systemic lupus erythematosus who received known efficacious therapy. All commonly used clinical variables significantly improved by week 4 but there was variation in responsiveness between them. BILAG-2004 and physician VAS had similar responsiveness to ultrasound variables but were more susceptible to observer bias. SRI-4 underestimated response, with substantial objective improvements in synovitis in SRI-4 non-responders. If replicated in larger studies these results may have implications for the design of clinical trials in SLE as well as routine clinical practice.

A problem in clinical trials in SLE has been that many therapies that appear to be effective in other contexts have produced negative results in randomised control trials. There are many possible causes for this, including the recruitment of some ANA-negative patients and use of active comparator arms. However, there are reasons to believe that choice of outcome measures is at least partly responsible for these discrepancies. In the belimumab programme, phase II data using the SELENA-SLEDAI were negative[409]. The SRI was derived from these phase II data and used to design a phase III trial that produced the opposite result [381]. The rituximab EXPLORER study was negative for its BILAG-based primary and secondary endpoints but had positive results in post hoc analyses such as BILAG A flare rate [410, 411]. While the SRI-4 has been highly successful in several clinical trials, in the two phase III trials of belimumab the response rate was rather low at 43-58% vs. 34-44% for belimumab and placebo[154]. The data I report here show that the SRI-4 underestimates clinical improvement in patients with arthritis and therefore may suggest that clinical trials would show higher response rates and greater differentiation of active and placebo arms if imaging outcome measures, or more responsive clinical outcome tools, were used.

In order to have effective treatment of SLE in the clinic, it is essential to be able to measure disease activity accurately, especially when using biologic therapies. An international task

force recently recommended treating to a target of low disease activity in SLE, as well as minimizing glucocorticoid exposure [402]. For the low disease activity target, it was recommended that a validated SLE disease activity index and/or by organ-specific markers be used. My results would support this, although this would need to be confirmed in longitudinal studies. I showed that patients with musculoskeletal disease who are not meeting SRI-4 or SLEDAI criteria may still have improvement, and physician VAS data suggest that overall physician judgment may be a better guide to response. Nevertheless, several other studies showed that patients with musculoskeletal symptoms but not clinical joint swelling (not meeting BILAG A/B or SLEDAI criteria) may have subclinical synovitis [121]. Hence, in forming their judgment of response physicians may wish to consider ultrasound in patients with ongoing inflammatory symptoms despite a degree of improvement.

Physician VAS appeared to be highly responsive in this study. It must be noted that assessors were not blinded to time point and this may affect subjective outcome measures due to observer bias. Observer bias may also affect the BILAG "improving" score, wherein synovitis that is still present but determined to be improving results in a lower BILAG score than if it is deemed stable or worsening. Further, the skill and experience of the assessor have effects on the BILAG score. All of our assessments were performed by trained assessors experienced in SLE clinical trials. An advantage of ultrasound is that it is more objective. However, it is operator-dependent and may be more difficult to standardize in multi-center studies. Joint counts were not as responsive as other instruments here, but are easier to standardize in multi-center studies given their widespread use in other inflammatory arthritis.

When first developed, the BILAG and SLEDAI were validated against physician's intention to treat and physician's judgment of overall disease activity. In my cross-sectional studyChapter 5:), I noted that ultrasound synovitis is common in patients without joint swelling and no clinical instrument could detect this. This suggests that validation against an objective measure of disease activity would be more valuable. Although there is no other study focusing specifically on musculoskeletal disease, one previous study compared the sensitivity to change of five

clinical instruments for overall disease activity (SLAM, SLEDAI, BILAG, ECLAM and LAI) [412]. Similarly, to this study, in that paper the SLEDAI was less responsive than the BILAG.

My results suggest that an organ-specific outcome measure may be more valuable in this common manifestation. This has already been established in the other second most common symptoms of SLE: cutaneous disease. The Cutaneous Lupus Activity and Severity Index (CLASI) [413] provides an organ-specific, continuous measure of cutaneous disease activity. In recent clinical trials of sifalimumab and anifrolumab, the CLASI showed a high rate of responsiveness [47, 414]. In this study, physician VAS was more responsive than the musculoskeletal component of the SLEDAI. Tender joint, swollen joint and symptomatic joint counts had similar responsiveness to the SLEDAI but may be advantageous in multicenter trials in being less dependent on the experience and opinion of the assessor, and less susceptible to observer bias. The data in this study and my previous larger cross-sectional study (Chapter 5:) demonstrate that joint counts and ultrasound findings vary more than BILAG and SLEDAI grades. It is therefore likely that a composite outcome measure could be designed for musculoskeletal disease that offers similar advantages to the CLASI. One previous paper has also shown the potential advantages of specific musculoskeletal outcome measures in patients treated with belimumab [415].

This study has some limitations. The number of patients was relatively small. Assessors were not blinded to therapy or time point, which may have affected some instruments. However, clinical and ultrasound assessors were blinded to each other's findings. Lastly, I have not yet assessed external responsiveness – i.e., responsiveness compared to some external anchor [407].

Despite these limitations, the results of this study are unique in comparing responsiveness to an objective standard and indicate the limitations of existing tools for musculoskeletal SLE. My results suggest that an organ-specific outcome measure for musculoskeletal disease would have advantages in both clinical trials and routine clinical practice. This is being

definitively assessed in the USEFUL study.

6.10 Conclusions:

In musculoskeletal-SLE, ultrasound was the variable most consistently sensitive to change. All commonly used clinical variables significantly improved by week 4 but there was variation in responsiveness between them. BILAG-2004 and physician VAS had similar responsiveness to ultrasound. SRI-4 underestimated response, with substantial objective improvements in synovitis in SRI-4 non-responders. Developing organ-specific outcome measures may improve the ability to measure treatment effects in SLE clinical trials.

6.11 Key messages:

1-Ultrasound was highly responsive for the musculoskeletal manifestations of systemic lupus erythematosus.

2-Most clinical outcome measures were less responsive than ultrasound; SLEDAI and SLE responder index 4 may underestimate response.

3- BILAG-2004 and physician visual analogue scales appeared more responsive than SLEDAI-2K and SLE responder index 4 for musculoskeletal SLE.

Chapter 7: USEFUL Study: prediction of response using baseline ultrasound

As discussed in detail in chapter 4, the key unmet need in SLE is identifying patients with active disease, given that these do not have swelling. We do not know whether ultrasound only synovitis is more responsive to therapy and therefore should be used to select patients for immunosuppressant or entry in to clinical trials.

7.1 Objective

Determine whether patients with abnormal musculoskeletal ultrasound have better clinical response to glucocorticoid therapy compared to patients with normal musculoskeletal ultrasound. Because the most responsive variable identified in the interim analysis was EMS VAS at 2 weeks, this forms the primary endpoint of the study.

7.2 Patients and methods

For the design of the USEFUL study please see 4.2.2. For the summary of recruitment please see 4.4.3. For baseline clinical and demographic characteristics, please see 4.4.1.

7.3 Statistical analysis

First, baseline characteristics of patients with active and inactive ultrasound were described using summary statistics. As planned in the protocol to analyse the efficacy of glucocorticoids in the patients with normal (inactive) and abnormal (active) ultrasound. Active ultrasound was defined as (GS ≥2 and or PD>0); otherwise it was defined as inactive. I used the early morning stiffness VAS (mm) at 2 weeks because this was the most responsive variable in the interim analysis. A predictive value of baseline ultrasound was concluded if there was differential response to treatment according to the presence of ultrasound inflammation. The difference between groups and associated 95% confidence interval were reported.

Early morning stiffness (EMS) VAS at week 2 was compared between patients with and without active ultrasound (GS≥2 and/or PD≥1 in at least 1 joint) at baseline using quantile

(median) regression, with cluster-robust standard errors used to account for clustering of patients within centres. Quantile regression was specified in the statistical analysis plan as an approach to analysing severely skewed variables which were not suited to parametric analysis. The primary analysis model adjusted for EMS VAS at baseline; the unadjusted difference is presented for comparison. In a sensitivity analysis, immunosuppression and oral steroid use (both recorded yes/no) were also added to the model. In a further sensitivity analysis, the above approaches were repeated in the per protocol set. In an additional, unplanned, sensitivity analysis, the above analyses were repeated in patients who were deemed unlikely to have fibromyalgia at baseline.

In addition to the sensitivity analyses detailed above to check the assumptions of the analysis model, the analysis of the primary efficacy variable will be repeated in the per protocol set.

Because there were a substantial number of patients with fibromyalgia, which may confound responses in SLE, we performed post-hoc analyses excluding patients with fibromyalgia for the most important endpoints.

7.4 Results

At baseline, 78 patients had active ultrasound (at least one joint with GS≥2 or PD>0) and 55 patients had inactive ultrasound. A comparison of the clinical response in these two groups is the main focus of this chapter.

7.4.1 *Patient disposition*

Patient disposition according to baseline ultrasound status is shown in (Table 7-1). There was no substantive difference in the completion of follow up between the two ultrasound groups. Overall, 91% of patients completed visit 6. 95% and 88% of the baseline ultrasound inactive and active groups completed.

Table 7-1: Patient disposition according to baseline ultrasound status

	All patients	US activity at baseline	
		Inactive	Active
	N=133	N=55	N=78
Baseline			
Attended	133/133 (100)	55/55 (100)	78/78 (100)
Week 2			
Attended	122/133 (92)	51/55 (93)	71/78 (91)
Withdrawn	2/133 (2)	1/55 (2)	1/78 (1)
Did not attend	5/133 (4)	1/55 (2)	4/78 (5)
Lost to follow-up	4/133 (3)	2/55 (4)	2/78 (3)
Week 6			
Attended	121/133 (91)	52/55 (95)	69/78 (88)
Withdrawn	4/133 (3)	1/55 (2)	3/78 (4)
Did not attend	3/133 (2)	0/55 (0)	3/78 (4)
Lost to follow-up	5/133 (4)	2/55 (4)	3/78 (4)

All values reported as n/N (%)

7.4.2 *Demographics*

Demographic data according to baseline ultrasound are shown in (Table 7-2). There were no significant differences between the groups in terms of age, disease duration and ethnicity. In the study there were seven males, all of them had active ultrasound at baseline. However, this is a small proportion of the study population which does not have a significant effect on the conclusion.

Table 7-2: Demographic data according to baseline ultrasound status:

	All patients	US activity at baseline		Difference (95% CI)	Test statistic, P value
		Inactive	Active		
	N=133	N=55	N=78		
Age (years) Mean (SD), range	46.1 (13.5), 17.0 to 78.0	47.9 (12.3), 25.0 to 76.0	44.8 (14.3), 17.0 to 78.0	3.1 (-1.6, 7.8)	t=1.32, p=0.190
Median (IQR)	47.0 (35.0, 55.0)	50.0 (36.0, 57.0)	45.0 (34.0, 54.0)		
Disease duration (y) Mean (SD), range	9.3 (8.9), 0.1 to 40.0	10.2 (9.8), 0.1 to 40.0	8.7 (8.1), 0.1 to 35.0	1.5 (-1.6, 4.5)	t=0.93, p=0.352
Median (IQR)	6.0 (2.0, 15.0)	7.0 (2.0, 17.0)	5.0 (2.0, 15.0)		
Sex n/N (%)					chisq=5.21, p=0.022
Male	7/133 (5)	0/55 (0)	7/78 (9)		
Female	126/133 (95)	55/55 (100)	71/78 (91)		
Ethnicity n/N (%)					chisq=6.06, p=0.195
White	82/133 (62)	40/55 (73)	42/78 (54)		
South Asian	34/133 (26)	11/55 (20)	23/78 (29)		
Black	14/133 (11)	3/55 (5)	11/78 (14)		
East Asian	1/133 (1)	0/55 (0)	1/78 (1)		
Other	2/133 (2)	1/55 (2)	1/78 (1)		

All values reported as n/N (%), IQR: interquartile rang, SD: slandered deviation

7.4.3 *Current medications*

Regarding the current medication history, no significant differences were noticed between the two groups (Table 7-3). This comparison was done because medications such as NSAIDs and glucocorticoid can affect ultrasound findings, although we asked them to discontinue their NSAIDs at least three days before the scan if possible and we restricted the dose of steroid to 5 mg or equivalent. In addition, there was no difference between the groups for the immunosuppressant and anti-malarial medications. This may suggest that the referring physician's intention to treat over previous months was not associated with ultrasound.

Table 7-3: Medication use according to ultrasound status

	All patients	US activity at baseline		Test statistic, P value
		Inactive	Active	
	N=133	N=55	N=78	
Antimalarial n/N (%)				
None	44/133 (33)	17/55 (31)	27/78 (35)	chisq=1.57, p=0.456
HCQ	88/133 (66)	37/55 (67)	51/78 (65)	
MEP	1/133 (1)	1/55 (2)	0/78 (0)	
Immunosuppressant n/N (%)				
None	93/133 (70)	38/55 (69)	55/78 (71)	chisq=5.75, p=0.125
Azathioprine	11/133 (8)	3/55 (5)	8/78 (10)	
Methotrexate	16/133 (12)	5/55 (9)	11/78 (14)	
Mycophenolate	13/133 (10)	9/55 (16)	4/78 (5)	
Regular biologics n/N (%)				
None	130/130 (100)	54/54 (100)	76/76 (100)	NA
NSAIDS n/N (%)				
None	106/133 (80)	43/55 (78)	63/78 (81)	chisq=8.13, p=0.421
Naproxen	11/133 (8)	6/55 (11)	5/78 (6)	
Ibuprofen	9/133 (7)	3/55 (5)	6/78 (8)	
Celecoxib	1/133 (1)	1/55 (2)	0/78 (0)	
Etodalac	1/133 (1)	0/55 (0)	1/78 (1)	
Etoricoxib	1/133 (1)	0/55 (0)	1/78 (1)	
Meloxicam	2/133 (2)	0/55 (0)	2/78 (3)	
Ibuprofen-cocodamol	1/133 (1)	1/55 (2)	0/78 (0)	
Ibuprofen-naproxen	1/133 (1)	1/55 (2)	0/78 (0)	
Daily oral glucocorticoids n/N (%)				
None	102/133 (77)	43/55 (78)	59/78 (76)	chisq=0.12, p=0.733
Prednisolone	31/133 (23)	12/55 (22)	19/78 (24)	

7.4.4 *How physicians identify inflammatory and non-inflammatory causes of pain*

For my last three baseline data analyses, I explored how well physicians were able to identify the cause of pain by examining their diagnoses of inflammatory features, fibromyalgia features and osteoarthritis features.

In the USEFUL study, physicians were asked to refer patients if they believe their pain was only inflammatory, therefore, warranting glucocorticoid treatment. At the baseline visit we asked clinicians to answer why they believed the pain was inflammatory. Details are shown in (Table 7-4). Interestingly, only a few of the inflammatory features were associated with ultrasound findings (swelling p=0.03, symmetry p=0.01) with trend for distribution (p=0.066), serology (p=0.09). Other classical inflammatory features such as morning stiffness, disease activity in other organs showed no association with objective joint inflammation.

Table 7-4: Baseline inflammatory features compared to ultrasound findings

	All patients	US activity at baseline		Test statistic, P value
		Inactive	Active	
	N=133	N=55	N=78	
EMS				
No	18/133 (14)	8/55 (15)	10/78 (13)	chisq=0.08, p=0.775
Yes	115/133 (86)	47/55 (85)	68/78 (87)	
Distribution				
No	20/133 (15)	12/55 (22)	8/78 (10)	chisq=3.37, p=0.066
Yes	113/133 (85)	43/55 (78)	70/78 (90)	
Symmetry				
No	12/133 (9)	9/55 (16)	3/78 (4)	chisq=6.16, p=0.013
Yes	121/133 (91)	46/55 (84)	75/78 (96)	
Swelling				
No	49/132 (37)	26/54 (48)	23/78 (29)	chisq=4.76, p=0.029
Yes	83/132 (63)	28/54 (52)	55/78 (71)	
Serology				
No	43/130 (33)	22/53 (42)	21/77 (27)	chisq=2.87, p=0.090
Yes	87/130 (67)	31/53 (58)	56/77 (73)	
Other lupus features				
No	67/133 (50)	29/55 (53)	38/78 (49)	chisq=0.21, p=0.649
Yes	66/133 (50)	26/55 (47)	40/78 (51)	
Prior therapy response				
No	46/133 (35)	16/55 (29)	30/78 (38)	chisq=1.25, p=0.263
Yes	87/133 (65)	39/55 (71)	48/78 (62)	
Jaccoud's arthropathy				
No	127/133 (95)	53/55 (96)	74/78 (95)	chisq=0.17, p=0.683
Yes	6/133 (5)	2/55 (4)	4/78 (5)	
Deformity				
No	127/133 (95)	53/55 (96)	74/78 (95)	chisq=0.17, p=0.683
Yes	6/133 (5)	2/55 (4)	4/78 (5)	
Other lupus inflammatory				
No	130/133 (98)	53/55 (96)	77/78 (99)	chisq=0.81, p=0.368
Yes	3/133 (2)	2/55 (4)	1/78 (1)	

The referring doctors were asked about the other musculoskeletal problems seen in SLE patients that may cause similar symptoms of pain (tables Table 7-5 and Table 7.6). However, none of these features was associated with having active ultrasound at baseline.

In summary, if patients with SLE presented with pain and physician needed to decide whether it is due to active musculoskeletal inflammation; the presence of swelling, symmetrical small joint distribution and serology appear to be helpful. But, presence fibromyalgia or Osteoarthritis features should not be used to rule out inflammatory joint pain.

Table 7-5: Baseline fibromyalgia features compared to ultrasound findings

	All patients	US activity at baseline		Test statistic, P value
		Inactive	Active	
	N=133	N=55	N=78	
Overall opinion of fibromyalgia				
No	101/133 (76)	41/55 (75)	60/78 (77)	chisq=0.10, p=0.752
Yes	32/133 (24)	14/55 (25)	18/78 (23)	
Fatigue				
No	102/132 (77)	43/55 (78)	59/77 (77)	chisq=0.04, p=0.833
Yes	30/132 (23)	12/55 (22)	18/77 (23)	
Waking unrefreshed				
No	108/132 (82)	46/55 (84)	62/77 (81)	chisq=0.21, p=0.647
Yes	24/132 (18)	9/55 (16)	15/77 (19)	
Cognitive symptoms				
No	112/132 (85)	48/55 (87)	64/77 (83)	chisq=0.43, p=0.511
Yes	20/132 (15)	7/55 (13)	13/77 (17)	
Somatic symptoms				
No	117/132 (89)	47/55 (85)	70/77 (91)	chisq=0.95, p=0.330
Yes	15/132 (11)	8/55 (15)	7/77 (9)	
Other fibromyalgia features present				
No	128/133 (96)	51/55 (93)	77/78 (99)	chisq=3.20, p=0.074
Yes	5/133 (4)	4/55 (7)	1/78 (1)	
Other fibromyalgia features (specify)				
None	128/133 (96)	51/55 (93)	77/78 (99)	
Generalised Tenderness	2/133 (2)	2/55 (4)	0/78 (0)	
Hyperalgesia	1/133 (1)	1/55 (2)	0/78 (0)	
IBS	1/133 (1)	1/55 (2)	0/78 (0)	
Postnatal depression	1/133 (1)	0/55 (0)	1/78 (1)	

Table 7-6: Baseline osteoarthritis features compared to ultrasound findings

	All patients	US activity at baseline		Test statistic, P value
		Inactive	Active	
	N=133	N=55	N=78	
Overall opinion of osteoarthritis N/n (%)				
No	97/133 (73)	39/55 (71)	58/78 (74)	chisq=0.19, p=0.659
Yes	36/133 (27)	16/55 (29)	20/78 (26)	
Hard tissue enlargement >1 joint N/n (%)				
No	106/131 (81)	41/54 (76)	65/77 (84)	chisq=1.48, p=0.224
Yes	25/131 (19)	13/54 (24)	12/77 (16)	
Hard tissue enlargement DIPs N/n (%)				
No	110/132 (83)	44/55 (80)	66/77 (86)	chisq=0.75, p=0.385
Yes	22/132 (17)	11/55 (20)	11/77 (14)	
Deformities consistent with OA N/n (%)				
No	118/132 (89)	49/55 (89)	69/77 (90)	chisq=0.01, p=0.924
Yes	14/132 (11)	6/55 (11)	8/77 (10)	
Previous radiographic evidence N/n (%)				
No	118/128 (92)	51/54 (94)	67/74 (91)	chisq=0.66, p=0.416
Yes	10/128 (8)	3/54 (6)	7/74 (9)	
Other OA features present N/n (%)				
No	127/132 (96)	53/54 (98)	74/78 (95)	chisq=0.94, p=0.332
Yes	5/132 (4)	1/54 (2)	4/78 (5)	
Other OA features (specify) N/n (%)				
None	127/131 (97)	53/54 (98)	74/77 (96)	
Trochanteric bursitis	1/131 (1)	0/54 (0)	1/77 (1)	
Hip pain	1/131 (1)	1/54 (2)	0/77 (0)	
Lumbar syno-dylosis as disc disease	1/131 (1)	0/54 (0)	1/77 (1)	
Symptoms consistent with OA	1/131 (1)	0/54 (0)	1/77 (1)	

7.4.5 *Baseline inflammatory features according to baseline ultrasound*

Although there were not many differences in features of fibromyalgia, osteoarthritis or baseline medications and demographics, as expected, patients with active ultrasound had many differences when inflammatory clinical features were compared. These are shown in (Table 7-7). Almost all of the features of musculoskeletal SLE activity were significantly worse in patients with active ultrasound. One interesting exception to this was the EMS minutes. Although this is commonly reported in inflammatory arthritis studies, in fact is very poor in comparison to an EMS VAS. In the analysis of the primary endpoint, the results of these parameters after treatment were compared after adjustment for the baseline differences.

Table 7-7: Baseline musculoskeletal SLE parameters according to baseline ultrasound status

	All patients	US activity at baseline		
		Inactive	Active	
	N=133	N=55	N=78	
EMS VAS (mm)	73.0 (57.0, 87.0), 0.0 to 100.0	67.0 (48.0, 83.0), 2.0 to 99.0	75.5 (63.0, 92.0), 0.0 to 100.0	z=-2.55, p=0.011
EMS duration (mins)	90.0 (30.0, 120.0), 0.0 to 600.0	70.0 (30.0, 120.0), 0.0 to 360.0	90.0 (30.0, 150.0), 0.0 to 600.0	z=-1.02, p=0.306
Tender 68 joint count	17.0 (7.0, 28.0), 0.0 to 68.0	15.0 (4.0, 27.0), 0.0 to 68.0	19.0 (10.0, 31.0), 0.0 to 68.0	z=-2.21, p=0.027
Swollen 66 joint count	1.0 (0.0, 4.0), 0.0 to 32.0	0.0 (0.0, 0.0), 0.0 to 10.0	3.0 (1.0, 6.0), 0.0 to 32.0	z=-6.52, p<0.001
Patient painful joint count	16.0 (9.0, 28.0), 0.0 to 42.0	11.0 (7.0, 20.0), 0.0 to 40.0	22.0 (14.0, 32.0), 1.0 to 42.0	z=-3.84, p<0.001
Physician MSK Disease Activity VAS (mm)	33.0 (21.0, 49.0), 0.0 to 90.0	24.0 (15.0, 36.0), 0.0 to 75.0	39.5 (30.0, 55.0), 13.0 to 90.0	z=-4.86, p<0.001
HAQ-DI score	1.4 (0.6, 2.0), 0.0 to 3.0	1.4 (0.3, 1.8), 0.0 to 2.8	1.4 (0.8, 2.1), 0.0 to 3.0	z=-1.82, p=0.069
Patient MSK disease activity VAS (mm)	65.0 (32.0, 79.0), 2.0 to 95.0	54.0 (28.0, 75.0), 7.0 to 92.0	70.5 (37.0, 81.0), 2.0 to 95.0	z=-1.87, p=0.061
MSK pain VAS (mm)	63.0 (47.0, 74.0), 5.0 to 99.0	57.0 (34.0, 69.0), 10.0 to 93.0	67.5 (53.0, 75.0), 5.0 to 99.0	z=-2.72, p=0.007
Total grey scale (joints)	5.0 (2.0, 9.0), 0.0 to 49.0	1.0 (0.0, 4.0), 0.0 to 10.0	7.0 (5.0, 11.0), 2.0 to 49.0	z=-7.67, p<0.001
Total power Doppler (joints)	0.0 (0.0, 1.0), 0.0 to 34.0	0.0 (0.0, 0.0), 0.0 to 0.0	0.0 (0.0, 2.0), 0.0 to 34.0	z=-6.00, p<0.001
Total osteophyte (joints)	0.0 (0.0, 0.0), 0.0 to 19.0	0.0 (0.0, 1.0), 0.0 to 8.0	0.0 (0.0, 0.0), 0.0 to 19.0	z=0.88, p=0.379
Total erosion score (joints)	0.0 (0.0, 0.0), 0.0 to 44.0	0.0 (0.0, 0.0), 0.0 to 1.0	0.0 (0.0, 0.0), 0.0 to 44.0	z=-1.86, p=0.063
Total OMERACT/EULAR GSPD score (joints)	5.0 (2.0, 9.0), 0.0 to 49.0	1.0 (0.0, 4.0), 0.0 to 10.0	7.0 (5.0, 11.0), 2.0 to 49.0	z=-7.67, p<0.001
Total amended OMERACT/EULAR GSPD score (joints)	4.0 (1.0, 7.0), 0.0 to 36.0	1.0 (0.0, 4.0), 0.0 to 10.0	6.0 (4.0, 9.0), 1.0 to 36.0	z=-6.51, p<0.001
Total grey scale (tendons)	0.0 (0.0, 1.0), 0.0 to 21.0	0.0 (0.0, 0.0), 0.0 to 7.0	0.0 (0.0, 2.0), 0.0 to 21.0	z=-3.52, p<0.001
Total power Doppler (tendons)	0.0 (0.0, 0.0), 0.0 to 20.0	0.0 (0.0, 0.0), 0.0 to 6.0	0.0 (0.0, 1.0), 0.0 to 20.0	z=-3.74, p<0.001
Total OMERACT/EULAR GSPD score (tendons)	0.0 (0.0, 1.0), 0.0 to 21.0	0.0 (0.0, 0.0), 0.0 to 8.0	0.0 (0.0, 2.0), 0.0 to 21.0	z=-3.51, p<0.001
Total amended OMERACT/EULAR GSPD score (tendons)	0.0 (0.0, 1.0), 0.0 to 20.0	0.0 (0.0, 0.0), 0.0 to 7.0	0.0 (0.0, 1.0), 0.0 to 20.0	z=-3.47, p=0.001
BILAG MSK score				
D/E	2/133 (2)	2/55 (4)	0/78 (0)	chisq=26.54, p<0.001
C	65/133 (49)	40/55 (73)	25/78 (32)	
B	52/133 (39)	10/55 (18)	42/78 (54)	
A	14/133 (11)	3/55 (5)	11/78 (14)	
SLEDAI MSK domain score				
0	55/133 (41)	36/55 (65)	19/78 (24)	chisq=22.46, p<0.001
4	78/133 (59)	19/55 (35)	59/78 (76)	

All values reported as median (IQR), range, except for BILAG MSK and SLEDAI MSK which are reported as n/N (%).

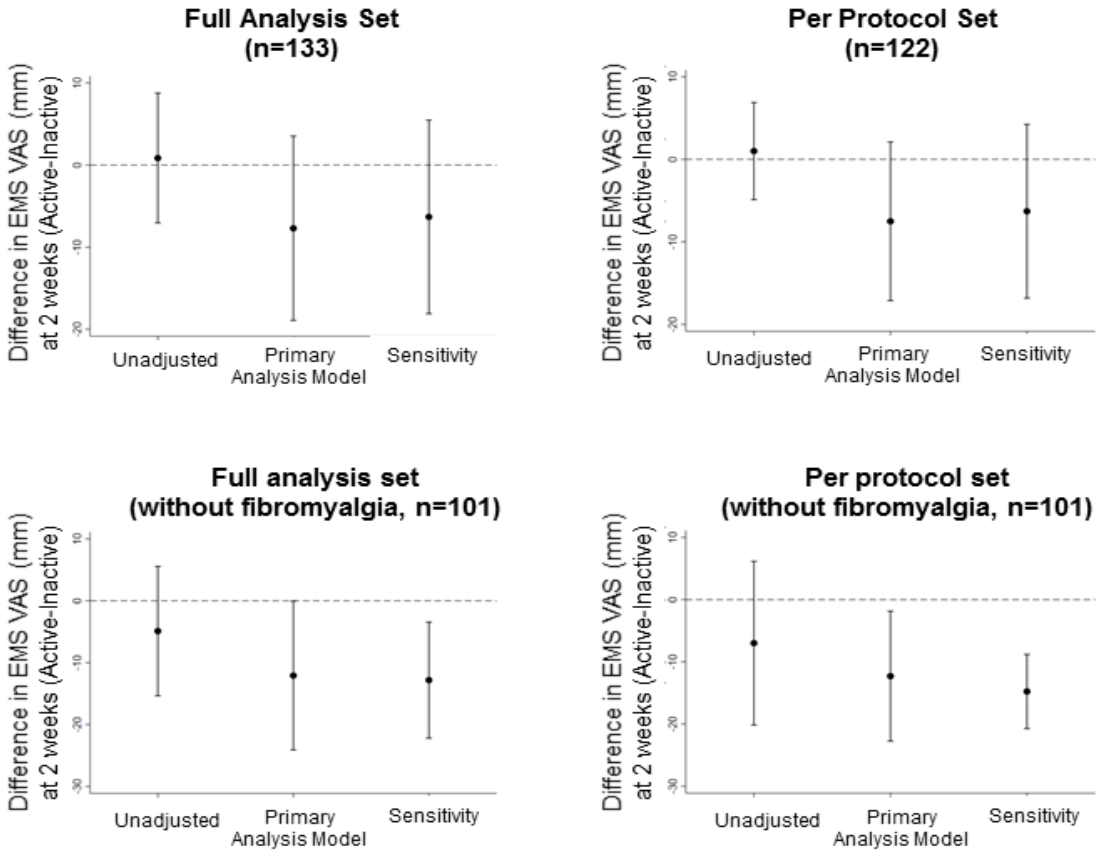
7.4.6 *Primary endpoint: EMS VAS*

Results of the primary endpoint are shown in Figure 7-1 and Table 7-8. As mentioned above, at baseline, the EMS VAS was 8.5mm higher in patients with active ultrasound compared to patients with inactive ultrasound. At 2 weeks, this was reversed: median EMS VAS had dropped to a greater extent in the patients with active ultrasound and after adjustment for baseline value was 0.85mm lower than for patients with inactive ultrasound (6.31mm after adjustment for immunosuppressant and oral steroids). Although these changes are in the direction hypothesised (i.e. if we believed that patients with baseline ultrasound activity would be more responsive), they are small and non-significant. The primary endpoint of the study was therefore not met, and this conclusion did not differ if a per-protocol set was analysed.

However, a substantial number (32 patients) had a clinician diagnosis of fibromyalgia at baseline. This is a condition that causes chronic pain and is not usually considered to be glucocorticoid-responsive. This may therefore confound the primary endpoint. I therefore repeated the analysis excluding these patients. When only analysing patients without fibromyalgia, the differences in adjusted and adjusted sensitivity analyses were significant.

Therefore, while this was not the prior analysis planned, these results suggest that in SLE patients in whom fibromyalgia has been clinically excluded, baseline ultrasound may be useful to select patients for immunosuppressive therapy.

Figure 7-1: Primary endpoint of USEFUL



The primary endpoint (EMS VAS) in all patients and in per protocol (there was no significant defences). After excluding patients with fibromyalgia (the differences in adjusted and adjusted sensitivity analyses were significant).

Table 7-8: Statistical table for primary endpoint

Population	US activity at baseline		Difference between medians (95% CI)		
	Inactive median (SE)	Active median (SE)	Unadjusted	Adjusted primary*, P value	Adjusted sensitivity**, P value
Full Analysis Set (FAS)	57.75 (4.09)	58.60 (5.86)	0.85 (-7.06, 8.76)	-7.70 (-18.92, 3.52), p=0.178	-6.31 (-18.10, 5.49), p=0.293
Per Protocol (PP)	58.00 (3.97)	59.00 (5.75)	1.00 (-4.88, 6.88)	-7.51 (-17.13, 2.11), p=0.126	-6.30 (-16.83, 4.24), p=0.241
FAS: No fibromyalgia	56.30 (4.53)	51.40 (6.01)	-4.90 (-15.36, 5.56)	-12.08 (-24.11, -0.06), p=0.049	-12.82 (-22.20, -3.44), p=0.007
PP: No fibromyalgia	57.00 (3.24)	50.00 (6.87)	-7.00 (-20.16, 6.16)	-12.30 (-22.76, -1.85), p=0.021	-14.78 (-20.75, -8.80), p<0.001

*Adjusted for baseline EMS VAS **Also adjusted for immunosuppressant and oral steroid use.

EMS=Early morning stiffness; VAS=Visual analogue scale

7.4.7 *Secondary endpoints: other musculoskeletal SLE parameters*

The other musculoskeletal SLE variables were then compared in a similar analysis. Results are shown in (Table 7-10) and (Figure 2-1). The physician VAS for musculoskeletal disease activity and global disease activity both showed significantly greater improvement in patients with active ultrasound at baseline. Also, there was a trend (p=0.070) to greater improvement in the MSK-BILAG, but not the SLEDAI. This is interesting as the BILAG was more concordant with ultrasound improvement and the primary endpoint (EMS VAS), and is therefore better able to detect the predictive value of ultrasound. It is important to note here that the physician who scored the VAS, SLEDAI and BILAG was blinded to all of the ultrasound scores. Lastly, there was significantly greater improvement in the ultrasound parameters themselves in patients with active ultrasound at baseline.

Table 7-9: Other Musculoskeletal SLE variables at 2 weeks according to baseline ultrasound status

Variable	US activity at baseline		Difference between medians (95% CI)		
	Inactive median (SE)	Active median (SE)	Unadjusted	Adjusted primary*, P value	Adjusted sensitivity**, P value
Tender 68 joint count	4.90 (0.79)	10.95 (1.65)	6.05 (2.74, 9.36)	-0.57 (-2.31, 1.17), p=0.521	-0.66 (-2.31, 0.99), p=0.427
Swollen 66 joint count	-0.00 (0.67)	1.00 (0.96)	1.00 (0.18, 1.82)	0.00 (-0.67, 0.67), p=0.995	0.00 (-0.67, 0.67), p=0.995
Patient painful joint count	6.50 (0.99)	14.50 (1.76)	8.00 (4.87, 11.13)	-0.93 (-4.44, 2.58), p=0.602	-0.76 (-4.49, 2.96), p=0.686
Physician MSK DA VAS (mm)	12.75 (1.79)	25.40 (2.47)	12.65 (7.85, 17.45)	7.07 (1.38, 12.77), p=0.015	7.08 (2.61, 11.55), p=0.002
HAQ-DI	1.16 (0.20)	1.32 (0.16)	0.16 (-0.18, 0.50)	0.01 (-0.05, 0.07), p=0.681	0.01 (-0.06, 0.09), p=0.746
Patient MSK DA VAS (mm)	48.45 (2.75)	48.10 (3.04)	-0.35 (-8.23, 7.53)	-1.58 (-10.11, 6.95), p=0.715	-4.16 (-13.73, 5.42), p=0.391
Patient MSK Pain VAS (mm)	41.95 (5.16)	54.20 (2.51)	12.25 (3.61, 20.89)	2.48 (-7.55, 12.50), p=0.627	1.05 (-10.94, 13.04), p=0.864
EMS (mins)	60.00 (17.87)	60.50 (11.75)	0.50 (-24.04, 25.04)	-4.16 (-19.44, 11.12), p=0.594	0.13 (-10.82, 11.09), p=0.981
Total GSPD (joints)	-0.00 (0.52)	3.95 (1.32)	3.95 (2.09, 5.81)	0.25 (-1.60, 2.09), p=0.793	0.25 (-1.60, 2.09), p=0.793
Total GSPD (tendons)>0	-0.00 (0.14)	2.80 (1.24)	2.80 (0.50, 5.10)	1.96 (0.88, 3.04), p=0.001	1.79 (-0.11, 3.68), p=0.064
Physician's global VAS (mm)	15.60 (1.96)	26.65 (1.67)	11.05 (6.27, 15.83)	6.99 (2.55, 11.43), p=0.003	7.02 (2.71, 11.33), p=0.002
Total BILAG score	1.85 (0.94)	3.10 (1.58)	1.25 (-1.61, 4.11)	0.00 (-1.49, 1.49), p=1.000	0.02 (-1.39, 1.43), p=0.977
Total SLEDAI score	2.20 (0.58)	5.25 (1.30)	3.05 (0.16, 5.94)	1.15 (-0.01, 2.31), p=0.051	1.05 (-0.22, 2.32), p=0.105
Patient general health VAS (mm)	49.70 (2.54)	54.10 (5.16)	4.40 (-4.80, 13.60)	2.19 (-10.02, 14.40), p=0.725	0.92 (-10.52, 12.36), p=0.874
Abnormal fatigue VAS (mm)	64.80 (2.50)	71.45 (1.59)	6.65 (1.02, 12.28)	-0.38 (-6.14, 5.38), p=0.897	-0.87 (-7.08, 5.35), p=0.784
	US activity at baseline		Odds ratio (95% CI)		
	Inactive %	Active %	Unadjusted	Adjusted primary*, P value	Adjusted sensitivity**, P value
BILAG MSK improved	28%	42%	1.85 (1.36, 2.52)	0.14 (0.02, 1.37), p=0.092	0.14 (0.02, 1.18), p=0.070
SLEDAI MSK improved	21%	21%	1.02 (0.27, 3.86)	0.74 (0.19, 2.89), p=0.660	0.72 (0.19, 2.72), p=0.627

*Adjusted for baseline EMS VAS **Also adjusted for immunosuppressant and oral steroid use. EMS=Early morning stiffness; VAS=Visual analogue scale

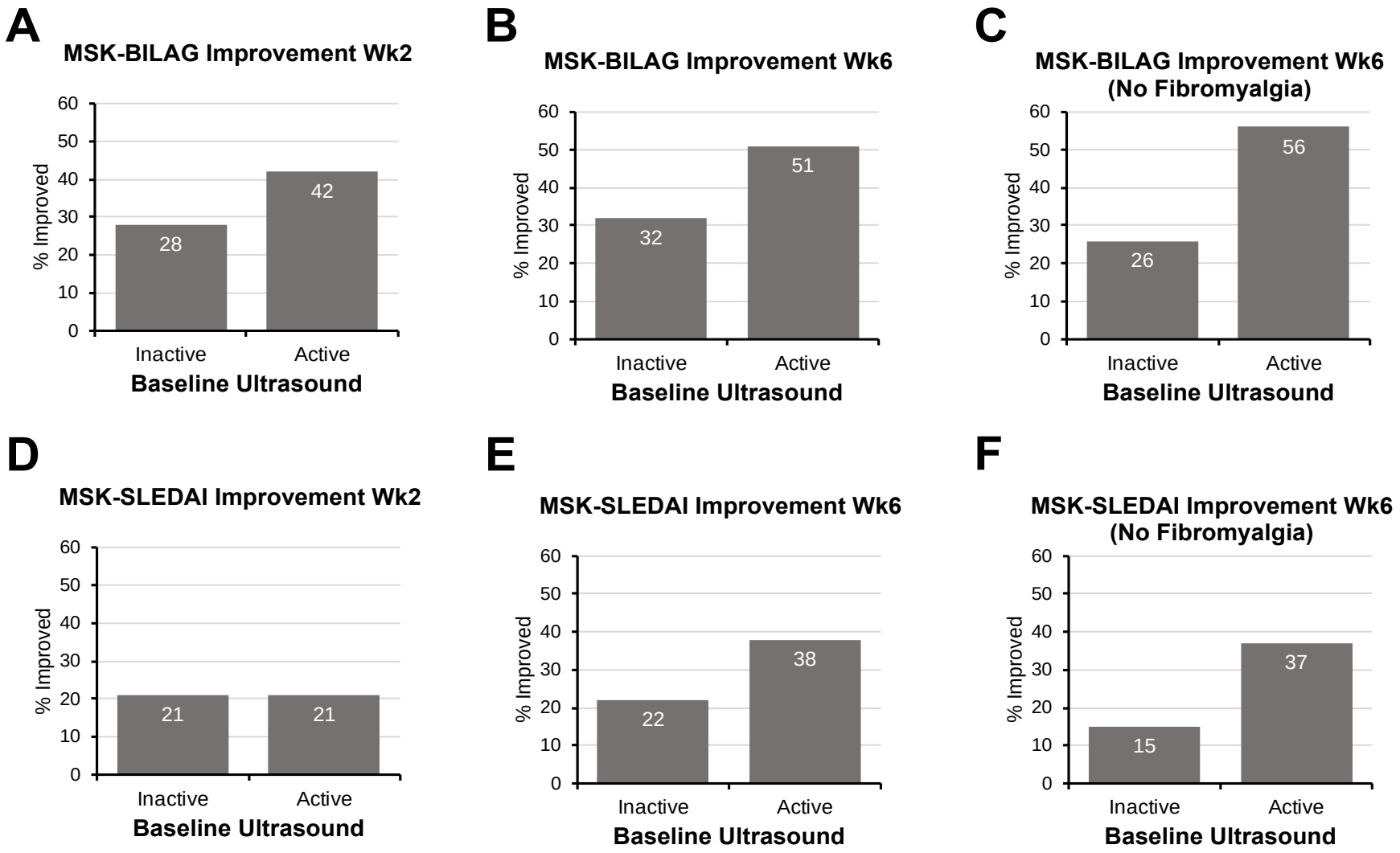
Given the results of the primary endpoint, I also repeated the analysis of secondary outcome measures in patients without fibromyalgia. The results are shown in (Table 7-10) and (Figure 7-2). After fibromyalgia patients were excluded, the differences in both BILAG and SLEDAI improvement were larger comparing patients according to baseline ultrasound status. Regarding BILAG (p=0.09), SLEDAI (p=0.06).

Table 7-10: Secondary clinical outcomes at 6 weeks (in patients without fibromyalgia)

Variable	US activity at baseline		Difference between medians (95% CI)		
	Inactive median (SE)	Active median (SE)	Unadjusted	Adjusted primary*, P value	Adjusted sensitivity**, P value
Tender 68 joint count	8.15 (2.50)	11.85 (2.23)	3.70 (-2.33, 9.73)	0.23 (-3.57, 4.03), p=0.903	0.53 (-4.01, 5.07), p=0.817
Swollen 66 joint count	3.65 (1.63)	6.65 (1.87)	3.00 (-0.56, 6.56)	1.07 (-2.61, 4.75), p=0.563	1.21 (-0.92, 3.34), p=0.257
Patient painful joint count	10.80 (3.17)	13.85 (1.90)	3.05 (-3.63, 9.73)	-2.61 (-6.75, 1.54), p=0.216	-1.58 (-6.54, 3.39), p=0.531
Physician MSK DA VAS (mm)	13.00 (2.58)	27.70 (4.79)	14.70 (4.91, 24.49)	1.00 (-7.28, 9.29), p=0.808	-0.09 (-7.54, 7.37), p=0.982
HAQ-DI	0.79 (0.24)	1.31 (0.16)	0.52 (-0.07, 1.10)	0.01 (-0.13, 0.14), p=0.922	0.02 (-0.12, 0.15), p=0.812
Patient MSK DA VAS (mm)	44.85 (7.00)	42.45 (4.91)	-2.40 (-22.68, 17.88)	-2.76 (-18.00, 12.47), p=0.719	-1.71 (-17.62, 14.20), p=0.831
Patient MSK Pain VAS (mm)	54.65 (4.12)	62.45 (3.02)	7.80 (-3.26, 18.86)	2.19 (-6.68, 11.07), p=0.623	0.07 (-11.90, 12.04), p=0.991
EMS VAS (mm)	60.30 (4.58)	66.25 (3.34)	5.95 (-2.84, 14.74)	1.89 (-5.87, 9.64), p=0.625	-1.64 (-10.07, 6.78), p=0.698
EMS (mins)	33.50 (9.93)	89.75 (14.11)	56.25 (34.61, 77.89)	0.26 (-27.89, 28.41), p=0.986	0.78 (-19.39, 20.95), p=0.939
Total GSPD (joints)	0.30 (0.85)	4.30 (1.68)	4.00 (1.14, 6.86)	-0.34 (-3.40, 2.72), p=0.826	-0.22 (-2.60, 2.15), p=0.854
Total GSPD (tendons)	1.75 (0.59)	5.65 (1.57)	3.90 (0.58, 7.22)	3.36 (0.14, 6.59), p=0.041	Model did not converge
Physician's global VAS (mm)	15.75 (2.63)	29.65 (4.42)	13.90 (3.77, 24.03)	-0.32 (-9.58, 8.95), p=0.945	-1.55 (-10.48, 7.38), p=0.729
Total BILAG score	2.00 (2.25)	5.40 (2.95)	3.40 (-2.97, 9.77)	-0.70 (-3.44, 2.03), p=0.614	-0.51 (-3.16, 2.14), p=0.704
Total SLEDAI score	3.75 (1.29)	3.85 (1.26)	0.10 (-1.73, 1.93)	-0.65 (-2.04, 0.73), p=0.348	-0.65 (-1.68, 0.39), p=0.219
Patient general health VAS (mm)	58.95 (4.12)	51.75 (2.82)	-7.20 (-16.51, 2.11)	-4.86 (-11.89, 2.18), p=0.175	-8.37 (-17.84, 1.10), p=0.083
Abnormal fatigue VAS (mm)	67.90 (3.48)	73.00 (4.52)	5.10 (-4.80, 15.00)	0.68 (-11.22, 12.58), p=0.909	0.07 (-10.94, 11.07), p=0.990
	US activity at baseline		Odds ratio (95% CI)		
	Inactive %	Active %	Unadjusted	Adjusted primary*, P value	Adjusted sensitivity**, P value
BILAG MSK improved	26%	56%	3.74 (2.03, 6.90)	1.91 (0.69, 5.26), p=0.213	2.17 (0.88, 5.34), p=0.091
SLEDAI MSK improved	15%	37%	3.24 (1.62, 6.50)	2.27 (1.08, 4.75), p=0.030	2.33 (0.96, 5.69), p=0.063

*Adjusted for baseline EMS VAS **Also adjusted for immunosuppressant and oral steroid use. EMS=Early morning stiffness; VAS=Visual analogue scale

Figure 7-2: BILAG and SLEDAI responses according to baseline ultrasound status



Comparison between BILAG and SLEDAI improvement according to the ultrasound status in the full set of patients and significant improvement when patients with fibromyalgia were excluded from the analysis.

7.4.8 *Quality of Life*

In week 2 results, all patients note there is only one variable of borderline significant (Burden to others). Quality of life domains that might be expected to correlate better with musculoskeletal disease activity (Physical health, Pain) did not differ according to baseline ultrasound.

Results were similar at week 6 with borderline difference for Physical health (P=0.050) and Body image (P=0.043) both were lower at week 6 in patients with active ultrasound. Results were also similar for the LQoL. However, for the musculoskeletal endpoint, Fibromyalgia may confound these results. I therefore repeated these analyses and excluding Fibromyalgia patients. After excluding fibromyalgia patients, the difference for Borden to others was far more significant (P=0.003) but there were still no other significant differences. Interestingly, at week 6 after excluding fibromyalgia patients, there was a significantly lower score for Quality of life Physical health in patients with active ultrasound at baseline(-7.49 (-12.90, -2.07), p=0.008.

Table 7-11: Secondary QoL outcomes at week 2(All patients)

Variable	US activity at baseline		Difference between medians (95% CI)		
	Inactive median (SE)	Active median (SE)	Unadjusted	Adjusted primary*, P value	Adjusted sensitivity**, P value
LupusQoL: Physical health	45.47 (4.64)	40.94 (5.18)	-4.53 (-17.36, 8.30)	-0.45 (-3.93, 3.03), p=0.799	-0.57 (-4.10, 2.95), p=0.749
LupusQoL: Pain	49.58 (5.33)	41.67 (4.61)	-7.92 (-16.91, 1.07)	0.65 (-3.84, 5.15), p=0.776	1.28 (-3.74, 6.30), p=0.616
LupusQoL: Planning	42.92 (5.78)	39.17 (6.02)	-3.75 (-16.56, 9.06)	-0.17 (-5.35, 5.00), p=0.948	-0.14 (-4.58, 4.31), p=0.951
LupusQoL: Burden to others	40.83 (7.80)	31.67 (7.87)	-9.17 (-28.60, 10.27)	-8.33 (-18.45, 1.78), p=0.106	-8.33 (-16.68, 0.01), p=0.050
LupusQoL: Emotional health	56.46 (5.41)	47.29 (5.12)	-9.17 (-21.04, 2.70)	0.05 (-3.30, 3.39), p=0.978	0.18 (-3.33, 3.68), p=0.922
LupusQoL: Body image	67.06 (4.33)	44.12 (8.93)	-22.94 (-43.38, -2.49)	-0.51 (-6.57, 5.54), p=0.867	-0.71 (-7.01, 5.58), p=0.823
LupusQoL: Fatigue	29.69 (8.39)	25.00 (4.71)	-4.69 (-17.43, 8.05)	1.42 (-3.41, 6.26), p=0.562	0.86 (-3.04, 4.75), p=0.665
LQoL	15.80 (1.34)	16.05 (1.42)	0.25 (-2.07, 2.57)	-0.35 (-1.93, 1.23), p=0.661	0.00 (-0.82, 0.83), p=0.993

Adjusted for baseline EMS VAS **Also adjusted for immunosuppressant and oral steroid use. EMS=Early morning stiffness; VAS=Visual analogue scale

Table 7-12: Secondary QoL outcomes at week 6

Variable	US activity at baseline		Difference between medians (95% CI)		
	Inactive median (SE)	Active median (SE)	Unadjusted	Adjusted primary*, P value	Adjusted sensitivity**, P value
LupusQoL: Physical health	44.58 (6.71)	35.47 (4.49)	-9.11 (-24.88, 6.65)	-6.57 (-13.27, 0.13), p=0.054	-7.25 (-14.48, -0.01), p=0.050
LupusQoL: Pain	52.50 (8.74)	40.83 (5.48)	-11.67 (-26.73, 3.40)	-5.22 (-13.60, 3.16), p=0.218	-3.07 (-10.18, 4.04), p=0.395
LupusQoL: Planning	57.92 (13.02)	41.67 (7.56)	-16.25 (-44.15, 11.65)	-1.75 (-9.93, 6.43), p=0.673	-2.22 (-9.63, 5.20), p=0.554
LupusQoL: Intimate relationship	37.50 (11.70)	30.00 (13.95)	-7.50 (-37.12, 22.12)	-0.42 (-9.01, 8.18), p=0.924	-0.63 (-8.92, 7.67), p=0.882
LupusQoL: Burden to others	40.83 (8.31)	30.00 (8.16)	-10.83 (-31.52, 9.85)	-7.54 (-15.27, 0.18), p=0.056	-5.67 (-11.68, 0.34), p=0.064
LupusQoL: Emotional health	57.08 (6.60)	39.79 (4.15)	-17.29 (-30.46, -4.12)	-3.61 (-9.09, 1.88), p=0.195	-2.60 (-8.44, 3.24), p=0.379
LupusQoL: Body image	68.33 (6.13)	44.87 (5.99)	-23.46 (-39.59, -7.33)	-8.83 (-16.65, -1.01), p=0.027	-7.95 (-15.64, -0.26), p=0.043
LupusQoL: Fatigue	29.38 (8.45)	25.31 (4.26)	-4.06 (-18.72, 10.59)	-2.56 (-8.15, 3.03), p=0.366	-2.78 (-7.95, 2.40), p=0.291
LQoL	12.85 (2.03)	17.30 (1.53)	4.45 (-0.76, 9.66)	-0.30 (-2.64, 2.04), p=0.801	0.23 (-1.29, 1.75), p=0.764

*Adjusted for baseline EMS VAS **Also adjusted for immunosuppressant and oral steroid use. EMS=Early morning stiffness; VAS=Visual analogue scale.
Due to failure of the analysis models to converge, possibly due to the large number of patients who said the domain was not applicable, data have not been provided for LupusQOL 4: Intimate relationship

Table 7-13: Secondary QoL outcome measures at week 2(in patients without fibromyalgia)

Variable	US activity at baseline		Difference between medians (95% CI)		
	Inactive median (SE)	Active median (SE)	Unadjusted	Adjusted primary*, P value	Adjusted sensitivity**, P value
LupusQoL: Physical health	48.28 (3.78)	43.44 (5.02)	-4.84 (-16.91, 7.22)	-1.37 (-5.58, 2.85), p=0.514	-0.93 (-5.33, 3.47), p=0.671
LupusQoL: Pain	52.92 (9.27)	41.67 (3.97)	-11.25 (-27.28, 4.78)	5.24 (-2.32, 12.79), p=0.167	3.61 (-2.22, 9.43), p=0.221
LupusQoL: Planning	48.33 (8.89)	42.08 (6.37)	-6.25 (-24.59, 12.09)	0.00 (-2.73, 2.73), p=1.000	0.43 (-3.83, 4.69), p=0.843
LupusQoL: Burden to others	42.08 (6.77)	36.67 (7.04)	-5.42 (-19.84, 9.00)	-8.33 (-13.57, -3.09), p=0.002	-7.85 (-12.96, -2.75), p=0.003
LupusQoL: Emotional health	53.54 (4.89)	51.04 (6.24)	-2.50 (-17.21, 12.21)	1.19 (-4.33, 6.70), p=0.671	1.57 (-3.64, 6.78), p=0.551
LupusQoL: Body image	66.69 (4.59)	45.31 (10.40)	-21.37 (-44.45, 1.70)	0.69 (-6.38, 7.75), p=0.846	-1.10 (-10.00, 7.81), p=0.805
LupusQoL: Fatigue	29.69 (6.04)	25.31 (3.72)	-4.38 (-15.84, 7.09)	1.89 (-3.49, 7.27), p=0.486	1.25 (-3.61, 6.10), p=0.613
LQoL	15.20 (1.43)	15.75 (2.04)	0.55 (-3.66, 4.76)	-0.70 (-2.28, 0.89), p=0.386	-0.50 (-1.72, 0.72), p=0.414

*Adjusted for baseline EMS VAS **Also adjusted for immunosuppressant and oral steroid use. EMS=Early morning stiffness; VAS=Visual analogue scale

Table 7-14: Secondary QoL outcomes at 6 weeks (in patients without fibromyalgia)

Variable	US activity at baseline		Difference between medians (95% CI)		
	Inactive median (SE)	Active median (SE)	Unadjusted	Adjusted primary*, P value	Adjusted sensitivity**, P value
LupusQoL: Physical health	45.52 (7.19)	34.53 (5.09)	-10.99 (-26.59, 4.61)	-7.74 (-14.47, -1.00), p=0.025	-7.49 (-12.90, -2.07), p=0.008
LupusQoL: Pain	52.50 (9.27)	37.92 (5.57)	-14.58 (-32.61, 3.45)	-7.09 (-16.12, 1.93), p=0.121	-4.49 (-14.43, 5.44), p=0.364
LupusQoL: Planning	64.17 (14.83)	42.08 (7.05)	-22.08 (-49.34, 5.17)	-1.84 (-10.70, 7.02), p=0.682	-1.71 (-9.61, 6.19), p=0.670
LupusQoL: Intimate relationship	41.87 (11.83)	40.00 (13.82)	-1.87 (-32.73, 28.98)	-0.00 (-5.16, 5.16), p=1.000	-0.00 (-6.02, 6.02), p=1.000
LupusQoL: Burden to others	45.00 (8.93)	29.17 (6.36)	-15.83 (-32.38, 0.71)	-8.36 (-16.05, -0.67), p=0.033	-6.68 (-13.28, -0.08), p=0.047
LupusQoL: Emotional health	57.50 (6.20)	42.71 (5.39)	-14.79 (-29.07, -0.52)	-2.96 (-9.39, 3.47), p=0.366	-0.41 (-6.38, 5.56), p=0.893
LupusQoL: Body image	68.04 (6.46)	44.06 (6.64)	-23.98 (-41.53, -6.43)	-9.02 (-20.08, 2.03), p=0.108	-7.72 (-16.46, 1.02), p=0.083
LupusQoL: Fatigue	35.00 (6.76)	25.94 (4.48)	-9.06 (-24.31, 6.19)	-4.29 (-12.27, 3.68), p=0.289	-3.96 (-12.57, 4.64), p=0.364
LQoL	12.65 (2.02)	17.15 (1.39)	4.50 (-0.39, 9.39)	-0.26 (-2.61, 2.09), p=0.827	-0.03 (-1.55, 1.48), p=0.967

*Adjusted for baseline EMS VAS **Also adjusted for immunosuppressant and oral steroid use. EMS=Early morning stiffness; VAS=Visual analogue scale

7.5 Discussion

Key findings of this study were:

When assessing SLE patients with suspected synovitis:

1. The presence of osteoarthritis or fibromyalgia features were a poor guide to whether ultrasound-confirmed synovitis would be present.
2. However, symmetry, swelling and probably distribution and serology were associated with ultrasound-confirmed synovitis.
3. The primary endpoint of the study was not met: we did not demonstrate a better clinical response to glucocorticoids in patients with ultrasound synovitis at baseline.
4. However, if fibromyalgia was excluded then ultrasound appeared predictive of clinical response to glucocorticoids.

In my literature review and published review article I highlighted the unmet need in this area (Figure 2-2.). It has been clear for some time that in patients with clinical synovitis, there is proven benefit of using glucocorticoids, immunosuppression and biologic therapies. It is also clear in many studies that there is a substantial proportion of patients (27% in my study) who have ultrasound proven synovitis without joint swelling, as well as a group with no ultrasound synovitis. It was not clear whether patients with ultrasound synovitis should be treated with glucocorticoids and immunosuppressant, while those without should be treated symptomatically. The results in this chapter provide an answer to this question.

When analysing the response to glucocorticoids, only physician's assessments of disease activity (VAS, BILAG and SLEDAI) showed a better response in ultrasound in active patients. Therefore, the primary endpoint of the study (early morning stiffness VAS at 2 weeks) was not met and none of the patient's reported outcomes showed greater improvement in patients with positive ultrasound. However, I found that the presence of fibromyalgia was a significant confounder. If patients with fibromyalgia were removed from the analysis, then baseline ultrasound was a significant predictor of response to glucocorticoids. It should be noted that

at baseline the presence of fibromyalgia was not helpful in predicting the likelihood of ultrasound synovitis at baseline. This is consistent with the clinical impression that this subgroup of patients had both inflammatory arthritis and fibromyalgia as independent causes of musculoskeletal pain. We may therefore interpret our responsiveness data as follows: ultrasound-proven synovitis predicts a better symptomatic response to glucocorticoids. However, if there is an additional, non-steroid responsive cause of pain present then the predictive effect of ultrasound cannot be detected.

There were two key limitations in this study. First, this was an open labelled single arm study. Therefore, there may be observation biases of physician and patient who were both aware that active treatment has been given. Secondly, the choice of glucocorticoid as a therapy. It is well known that glucocorticoids are effective for many types of arthritis and this includes osteoarthritis. It remains possible that baseline ultrasound would provide more response to SLE specific therapy such as azathioprine or rituximab.

My results have implications for both clinical trials and routine practice. In clinical trials that focus on musculoskeletal SLE then I would advise fibromyalgia as an exclusion criterion, since it will not be possible to detect the efficacy of SLE medications in patients with this problem. In routine practice, my results indicate that an ultrasound scan should be considered in SLE patients with joint pain but no clinical synovitis. If these patients have positive ultrasound then they should be considered for escalation of immunosuppressive therapy (not just glucocorticoids).

Chapter 8: USEFUL Study: Responsiveness of ultrasound and clinical variables

The purpose of this chapter is to further evaluate the responsiveness of ultrasound compared to other clinical variables.

In my pilot study (Chapter 6:), most of the patients had clinical synovitis at baseline. If we propose to include patients with ultrasound-only synovitis in clinical trials and for immunosuppressive therapy in routine practice, then it is necessary to assess the responsiveness of outcome measures in the USEFUL population that includes patients with ultrasound synovitis or no synovitis.

Also, in the pilot study I found that ultrasound had greater overall responsiveness than many of the other variables. However, we don't know whether this is clinically significant. In other words, the responsiveness of ultrasound may be *too* great, suggesting that patients have improved when in reality they still have symptoms and are at risk of long-term damage. This is analogous to measuring a reduction in CRP after glucocorticoids – a reduction may occur even if the cause of the raised CRP was infection, and does not necessarily indicate that the patient is getting better. In the context of ultrasound in SLE, over-responsiveness could occur if there was significant autoimmune-mediated pain that was not captured by the ultrasound, e.g. if it was in a joint not included in the scan or a pathology that is not well visualised on ultrasound such as bone oedema.

There are several ways that the clinical significance of ultrasound response could be investigated: against symptoms, against longer term outcomes, or in differentiating treatment arms in a randomised trial. Given the design of the USEFUL study, I investigated the relationship of ultrasound-response to patient-reported improvement in pain.

8.1 Objective

- Determine whether musculoskeletal ultrasound variables (GS or PD) are responsive to therapy than other outcome measures.

- Determine the overall effect size of change in ultrasound in a broader population of patients who don't all have swollen joints
- To compare the responsiveness of ultrasound and other musculoskeletal variables with patient-reported improvement in pain

8.2 Patients and methods

For the design of the USEFUL study please see 4.2.2. For a summary of recruitment please see 4.4.3. For baseline clinical and demographic characteristics, please see 4.4.1.

8.3 Statistical analysis

To test whether total ultrasound scores for GS, PD and tenosynovitis were sensitive to change, changes in each of these variables were correlated with the responses on the Likert scale for improvement using Kendall's tau-a. Median differences between each of the tau-a values calculated for the ultrasound variables and those calculated for the clinical variables, together with bootstrapped confidence intervals, were obtained. These analyses were conducted in all patients in the primary analysis; a sensitivity analysis restricted the analysis to patients with active ultrasound present at baseline. This correlation approach was adopted because it was likely that there would be variation in the extent of response to Depo-medrone. In addition, as a sensitivity analysis, effect sizes were calculated using the standardized test statistic Z from Wilcoxon signed ranks tests of differences between baseline and each post-baseline visit, according to the formula r=Z/sqrt(n1+n2). Effect sizes have been assessed using Cohen's criteria as large (|r|>0.5), medium (|r|>0.3) or small (|r|>0.1).

Within categories of the musculoskeletal domains of the existing instruments (SLEDAI-2K MSK score 0 or 4; BILAG (2004) A, B, C, D/E) descriptive summaries (mean, SD, median, IQR, minimum, maximum) were obtained for each of the following musculoskeletal-specific variables at baseline: tender joint count (68 joints), swollen joint count (66 joints), patient's painful joint count, patient pain VAS, patient musculoskeletal disease activity VAS, physician musculoskeletal disease activity VAS, health assessment questionnaire disability index (HAQ-

DI), severity of early morning stiffness VAS, duration of early morning stiffness, total scores for ultrasound grey scale, power Doppler and tenosynovitis and ultrasound-detected presence of osteophytes in the hands and wrists.

The following non-specific outcomes were summarised at baseline within categories of the musculoskeletal domains of the existing instruments (SLEDAI-2K MSK score 0 or 4; BILAG (2004) merged ABC vs DE), further split by the categories of any other domains found to be involved in at least 12 patients (a minimum usually stipulated for accurate estimation of a quantity in pilot studies): physician's global VAS, patient fatigue VAS, erythrocyte sedimentation rate (ESR), Ig titres, complement titres.

8.4 Results

8.4.1 *Overall responsiveness of the clinical and ultrasound musculoskeletal variables*

The overall responsiveness in the ultrasound and clinical variables at 2 and 6 weeks is shown using effect sizes in Table 8-1. In keeping with my pilot study in 20 patients, some of the largest effect sizes were seen for physician VAS, BILAG and ultrasound parameters. However, there were some differences in the USEFUL patients. At week 2, the effect size for ultrasound was "medium", but had been "large" in my pilot study. This can be explained by the large number of patients in USEFUL with normal ultrasound scores at baseline. Similarly, the patient VAS was less responsive in USEFUL than in the pilot study, which may be because glucocorticoids are less effective in patients without synovitis.

At week 6, the effect sizes for BILAG and SLEDAI were both medium in USEFUL. In the pilot study BILAG had a large effect size at week 4. This differences may also be due to the lower frequency of clinical synovitis in USEFUL. Patients without swollen joints score BILAG C at baseline and could only improve to BILAG D if they achieved complete remission. In contrast, patients with severe (BILAG A) or moderate (BILAG B) synovitis at baseline can reduce their scores by one grade if these features are "improving" at follow up.

Table 8-1: Signed rank effect sizes for changes at weeks 2 and 6

Variable	All patients		Baseline US active only	
	Week 2	Week 6	Week 2	Week 6
EMS VAS (mm)	0.33 (Medium)	0.29(Small)	0.37 (Medium)	0.29 (Small)
EMS mins (min)	0.19 (Small)	0.11(Small)	0.24 (Small)	0.11 (Small)
Tender 68 joint count	0.37 (Medium)	0.26(Small)	0.35 (Medium)	0.27 (Small)
Swollen 66 joint count	0.32 (Medium)	0.21(Small)	0.43 (Medium)	0.30 (Medium)
Patient painful joint count	0.33 (Medium)	0.29(Small)	0.37 (Medium)	0.40 (Medium)
Physician MSK DA VAS (mm)	0.50(Large)	0.38(Medium)	0.51 (Large)	0.40 (Medium)
HAQ-DI	0.19(Small)	0.16(Small)	0.23 (Small)	0.19 (Small)
Patient MSK DA VAS (mm)	0.24(Medium)	0.20(Small)	0.27 (Small)	0.26 (Small)
Patient MSK Pain VAS (mm)	0.28(Small)	0.16(Small)	0.32 (Medium)	0.20 (Small)
BILAG MSK	N/A	0.31(Medium)	N/A	0.39 (Medium)
SLEDAI MSK	N/A	0.27(Small)	N/A	0.39 (Medium)
Total GSPD (joints)	0.33(Medium)	0.33(Medium)	0.43 (Medium)	0.41 (Medium)
Total GSPD (tendons)	0.13(Small)	0.10(Small)	0.14 (Small)	0.13 (Small)

EMS: early morning stiffness, HAQ: Health Assessment Questionnaire, VAS: visual analogue scale, BILAG British Isles Lupus Assessment Group. SLEDAI: Systemic Lupus Erythematosus Disease Activity Index.

8.4.2 *Patient-reported change in pain*

I next examined the patient-reported change in pain using the Likert scale. Estimated proportions of patients within each category for change in pain are shown in (Table 8-2). At week 2, 62% of the patients reported they improved, and 61% at week 6. On the other hand, 11% said they got worse by week 2 and 14% at week 6. A quarter reported no change in their situation in both week 2 and week 6. These results therefore also highlight that the most responsive variables may not necessarily be the most accurate (since some patients felt worse). It is also important to note that patient reported change in pain may relate to any cause, while ultrasound and physicians attempt to specifically assess pain due to SLE.

Table 8-2: Estimated proportions of patients in each category for change in pain Likert scale

Change	Week2	Week6
A very great deal better	0.03	0.06
A great deal better	0.04	0.05
A good deal better	0.14	0.11
Moderately better	0.06	0.05
Somewhat better	0.11	0.07
A little better	0.17	0.22
Almost the same, hardly better	0.07	0.05
About the same	0.27	0.25
Almost the same, hardly worse	-	0.04
A little worse	0.03	0.03
Somewhat worse	0.02	0.03
Moderately worse	0.04	-
A good deal worse	0.02	0.02
A great deal worse	-	0.01
A very great deal worse	-	0.01

8.4.3 *Correlation of change in ultrasound with patient Likert responses*

The correlations between each clinical or ultrasound variable and the patient's Likert responses are shown in (Table 8-3). The values are Kendall's Tau. The first two columns show the overall correlations at weeks 2 and 6. These correlations are generally quite weak. The only strong correlations were seen for other patient-reported variables (EMS VAS and duration, and musculoskeletal pain VAS) at week 2, as expected. The correlations between ultrasound variables and patient's Likert response are very weak. The other columns in the table provide a formal comparison of the strength of correlation for ultrasound parameters with each of the clinical variables.

Table 8-3: Correlation of clinical and ultrasound variables with patient's Likert response

Variable	Correlation with change in pain		Difference (95% CI)			
	Week 2 (95% CI)	Week 6 (95% CI)	cf. GSPD (joints) W2	cf. GSPD (joints) W6	cf. GSPD (tendons) W2	cf. GSPD (tendons) W6
EMS VAS (mm)	0.26 (0.17, 0.35)	0.16 (0.04, 0.29)	-0.22 (-0.35, -0.09)	-0.13 (-0.31, 0.04)	-0.27 (-0.38, -0.15)	-0.16 (-0.31, 0.00)
EMS duration (mins)	0.20 (0.09, 0.31)	0.12 (0.00, 0.23)	-0.16 (-0.32, 0.01)	-0.08 (-0.23, 0.06)	-0.20 (-0.34, -0.07)	-0.11 (-0.26, 0.04)
Tender 68 joint count	0.01 (-0.09, 0.11)	0.15 (0.04, 0.26)	0.03 (-0.12, 0.19)	-0.12 (-0.27, 0.03)	-0.01 (-0.14, 0.11)	-0.14 (-0.28, -0.01)
Swollen 66 joint count	-0.08 (-0.18, 0.02)	0.07 (-0.03, 0.17)	0.12 (-0.03, 0.28)	-0.04 (-0.17, 0.10)	0.07 (-0.03, 0.18)	-0.06 (-0.19, 0.06)
Pt painful joint count	0.16 (0.04, 0.27)	0.13 (0.01, 0.24)	-0.11 (-0.24, 0.02)	-0.10 (-0.24, 0.05)	-0.16 (-0.28, -0.04)	-0.12 (-0.26, 0.02)
Phys MSK VAS (mm)	0.06 (-0.05, 0.17)	0.13 (0.02, 0.23)	-0.01 (-0.17, 0.14)	-0.09 (-0.22, 0.04)	-0.06 (-0.18, 0.06)	-0.12 (-0.25, 0.01)
HAQ-DI	0.10 (-0.02, 0.22)	0.10 (0.00, 0.20)	-0.05 (-0.19, 0.09)	-0.07 (-0.22, 0.09)	-0.10 (-0.25, 0.05)	-0.09 (-0.22, 0.04)
Patient MSK VAS (mm)	0.08 (-0.04, 0.20)	0.10 (-0.01, 0.22)	-0.04 (-0.19, 0.12)	-0.07 (-0.22, 0.08)	-0.09 (-0.24, 0.06)	-0.09 (-0.21, 0.02)
Patient Pain VAS (mm)	0.28 (0.17, 0.39)	0.16 (0.05, 0.27)	-0.24 (-0.39, -0.09)	-0.13 (-0.28, 0.03)	-0.28 (-0.41, -0.16)	-0.15 (-0.29, -0.01)
BILAG MSK	0.05 (-0.05, 0.14)	0.08 (-0.02, 0.18)	0.00 (-0.13, 0.13)	-0.05 (-0.18, 0.09)	-0.05 (-0.17, 0.08)	-0.07 (-0.20, 0.06)
SLEDAI MSK	0.05 (-0.03, 0.14)	0.13 (0.05, 0.22)	-0.01 (-0.13, 0.11)	-0.10 (-0.24, 0.04)	-0.06 (-0.17, 0.05)	-0.13 (-0.24, -0.01)
Total GSPD (joints)	0.04 (-0.08, 0.17)	0.03 (-0.08, 0.15)	-	-	-0.05 (-0.20, 0.10)	-0.02 (-0.15, 0.11)
Total GSPD (tendons)	0.00 (-0.09, 0.09)	0.01 (-0.08, 0.09)	0.05 (-0.10, 0.20)	0.02 (-0.11, 0.15)	-	-

EMS: early morning stiffness, VAS: visual analogue scale, BILAG British Isles Lupus Assessment Group. SLEDAI: Systemic Lupus Erythematosus Disease Activity Index.

8.5 Discussion

In terms of clinical trials, one of the most important characteristics of an outcome measure is responsiveness. Most of the validated instruments in current use have been validated as responsive. For example, the BILAG was shown to be sensitive to change when compared to change in therapy [416].

However, there are far fewer studies that formally compare the different instruments with each other. Also, there are fewer studies that use a formal longitudinal design where all patients receive the same therapy. Lastly, there have generally been no objective measures of disease activity against which to compare the responsiveness of various clinical tools.

In this study I addressed all of these needs. My results confirmed my pilot data in demonstrating very different levels of responsiveness in the different outcome measures, and these results will be useful in choosing which variables should be analysed in clinical trials. Where the results in this chapter differed from my previous study, this can be attributed to the greater amount of synovitis at baseline in the earlier study.

The results were less clear when it came to comparing ultrasound responses to patient Likert responses. The correlation between these variables was poor. Although this was the protocol-specified analysis, these results may not be unexpected given the baseline data in the study. Baseline ultrasound findings showed that many patients had significant pain that was not due to synovitis. This may be due to other pathologies like osteoarthritis and fibromyalgia that will not respond as well to glucocorticoids. When answering the patient's Likert scale, the patients would report this pain, even if it was non-inflammatory. Hence the ultrasound tool that relates only to objective synovitis could differ.

Given this interpretation, it remains possible that ultrasound response has other types of clinical significance apart from representing patient experience. Ultrasound may capture only the response in SLE pathology, and this may have implications for longer-term outcomes. For example, long term damage and quality of life outcomes may be better predicted by ultrasound

response to therapy. Ultrasound responses may also be better when comparing immunosuppression and placebo treatment arms of a clinical trial.

Previous data in rheumatoid arthritis are consistent with this hypothesis. Most analyses of disease activity in rheumatoid arthritis are based on the DAS28, which includes the "objective" parameters, swollen joint count and CRP, as well as the patient-reported parameters, tender joint count and VAS. The patient-reported outcomes used in RA may have the same issues as in my SLE study – they may reflect other types of pain, not just autoimmunity. A recent study compared the DAS28 with an analysis of disease activity using only the objective components. In that study, an outcome measure based only on the swollen joint count and CRP predicted erosions better than the DAS28 [417].

The results in this chapter, as well as the previous chapter, will be used in two future projects. First, we will use this data to design a new composite outcome measure for musculoskeletal SLE. Second, we will analyse these variables and the new outcome measure in a feasibility RCT ("ROOTS"). Thereby we expect to be able to design more robust clinical trials in musculoskeletal SLE, with smaller sample sizes.

Chapter 9: MISTER study: Validation of ultrasound using MRI as the imaging gold standard in SLE (Criterion validity)

9.1 Objective

1. To validate ultrasound-only synovitis using MRI
2. To describe MRI pathology in patients with SLE arthritis in detail

9.2 Patients and methods

(MISTER: Mri In Sle arThRitis) is a cross-sectional observational study was conducted in patients with Systemic Lupus Erythematosus. All of the patients were ANA positive. Patients with positive Anti-CCP and RF positive (ever) were excluded. Also, patients must be on a stable dose of immunosuppressant over the last three months. Patients were asked to stop NSAIDs at least three days before the scan if possible. The maximum allowed dose of glucocorticoids allowed was 5 mg.

All individuals provided informed written consent and this research was carried out in compliance with the Declaration of Helsinki. The study was approved by National Research Ethics Committee Yorkshire and Humber–Leeds East reference 10/H1306/88. All procedures were performed in accordance with relevant guidelines and regulations. The University of Leeds was the sponsorship.

Although the planned total recruitment is 52 patients, an interim analysis has been presented here. A total of 36 of SLE patients fulfilling SLICC 2012 criteria were recruited in this study. Two patients had their MRI scan done without contrast. Patients were divided into three groups. The first group consisted of 11 patients with pain (arthralgia), no swelling, and normal ultrasound. The second group comprised of 14 patients with arthralgia and ultrasound synovitis (GS≥2, PD>0) or tenosynovitis (GS≥1 and/or PD>0). The third group comprised 11 with clinical synovitis (swelling) of whom 8/11 had abnormal ultrasound scans. All of these patients underwent MRI and ultrasound scans (hand and wrist) in the most symptomatic hand (the use of single hand is more comfortable for patients, reduce time and

cost of the scan) on the same day in addition to clinical assessments performed by trained rheumatologists who are blinded to the ultrasound assessment.

9.3 Clinical and laboratory assessments

SLE was assessed by using BILAG-2004 [169], SLEDAI-2K 30 days[388] Joint disease was assessed using nine tender and swollen joint counts (Wrist,MCP2-5,PIP2-5 to match the joints evaluated by the MRI scan and ultrasound), symptomatic joint count, physician musculoskeletal visual analogue score (VAS), patient's pain VAS and minutes of early morning stiffness. Patients were tested for routine inflammatory and serological markers. CRP (mg/l), ESR (mm/h), RF (IU/ml), CCP antibodies (CCP, IU/ml), complements (C3 and C4, g/l), ANA, extracted nuclear antibodies including anti-dsDNA, anti Ro, anti La, anti-chromatin, anti Sm, anti-RNP and immunoglobulins (IgA, IgM, IgG,) were measured on the visit date in an accredited clinical diagnostic laboratory.

9.4 Ultrasound assessment

Ultrasonography (grey scale (GS) and power Doppler (PD)) was performed using high resolution ultrasound machines; General Electric (GE Healthcare, Chicago, IL) Logiq E9 ultrasound with multi-linear 6–15 MHz transducer. Wrist and hand were assessed in all patients. Joints in the hand and wrist were examined using a standard approach of examining the following; radio-carpal, inter-carpal, ulnar-carpal joints and second to fifth MCP joints and second to fifth PIP joints. Tendon sheaths including the first to sixth extensor tendons compartments of the wrist and second to fifth flexor digitorum tendon sheaths of the hands were assessed for tenosynovitis. For more details, please see 4.1.

9.5 MRI scoring of arthritis:

Patients have been consented to have an MRI scan of the wrists and hands. The MRI machine was a 3T Siemens VERIO scanner. The MRI protocol consisted of T1 (axial, coronal), T2 fat-saturated axial and STIR (short-tau inversion recovery) and T1 volumetric interpolate breath-hold (VIBE) 3D pre-contrast and post contrast coronal. MRI scans were

obtained using standard musculoskeletal sequences with gadolinium contrast. Semiquantative scoring of the images used the OMERACT for assessing activity in Rheumatoid Arthritis, (RAMRIS) [418].

The RAMRIS scores bone marrow oedema (23 anatomical areas, (range 0-3), synovitis (7 anatomical areas, (range 0-3), erosions (23 anatomical areas, (range 0-10) and tenosynovitis was scored in 10 anatomical areas (range 0-3). I modified the score to match the joint areas assessed clinically and by ultrasound. So, there were 24 anatomical areas for both bone marrow oedema and erosion with total score of 51 for each variable. For synovitis there were 11 areas with total score of 33 and 13 areas for tenosynovitis with total score of 39. The maximum total score for my modified RAMRIS is 123.

9.6 Statistical analysis:

General clinical characteristics were described for each of the three groups: (1) arthralgia with normal ultrasound and examination; (2) arthralgia with ultrasound synovitis and normal examination, also called “subclinical synovitis”; (3) arthralgia with joint swelling, of whom most had ultrasound-confirmed synovitis.

RAMRIS score for synovitis was the key criterion for comparing the groups and was compared between these groups using a Mann-Whitney U test with pairwise comparisons. The other RAMRIS scores (bone oedema, tenosynovitis and erosions) were also compared as secondary endpoints.

The agreement between ultrasound and MRI synovitis at each site (joint or tendon sheath) was tested by calculating sensitivity, specificity, Kappa and PABAK statistics. Level of agreement between MRI and ultrasound when detecting synovitis was quantified as the proportion of joints in which both methods exactly agreed over the presence or absence of synovitis (percentage exact agreement [PEA]), proportions of category-specific negative and positive agreement (Sp0 and Sp1 for absence and presence of synovitis, respectively), and the proportions of joints where MRI and ultrasound disagreed in either direction (US>MRI,

US<MRI). One common criticism is that kappa is highly dependent on the prevalence of the condition in the population. The kappa statistic was therefore supplemented with the prevalence-adjusted bias-adjusted kappa (PABAK) to give an indication of the extent to which differences in the overall level of synovitis identified by each assessment method together with imbalances in the proportions of joints with and without synovitis affected the calculated value of kappa. PAB AK has been employed in many previous studies for agreement assessment[419]. Compared with kappa, PABAK reflects the ideal situation, and ignores the variation of prevalence across the conditions and bias presented in the "real" world. Finally, qualitative features of the imaging were described by an experienced radiologist.

9.7 Results

A total of 36 patients were enrolled, of whom, two were males and 34 females. The mean of the age for all patients was 44.3(SD 12) years. Disease duration mean was 72(SD 79) months. Most of the patients were Caucasians 25/36 (69%), 6/36 (17%) were south Asians. Eight patients were taking glucocorticoids and 26 patients were on hydroxychloroquine. Other baseline variables are detailed in (Table 9-1).

Table 9-1: Baseline clinical characteristics of patients in MISTER study

	All patients	Normal US	Clinical synovitis± US	US-synovitis
No. of patients	36	11	14	11
Age mean(SD)	44.3(12)	42(13)	44(14)	46(12)
Disease Duration in months mean(SD)	72(79)	36(12-56)*	26(12-84)*	54(2-87)*
TJC (0-9)*	4(1-6)	2(1-4)	5(0-9)	5(4-8)
SJC (0-9)*	2(2-3)	0(0-0)	3(2-5)	0(0-0)
Physician VAS*	35.5(14-54)	18(16)	41(19)	42(18)
Patient's pain VAS*	68(36-85)	10(2-29)	43(27-55)	43(28-58)
Symptomatic Joint count*	17(7-27)	18(2-23)	20(16-31)	16(8-20)
Steroid (%)	8/36(22%)	3/11(27%)	2/14(14%)	3/11(27%)
DMARDs naïve (%)	4/36(11%)	1/11(9%)	2/14(14%)	1/11(9%)
EMS(minutes)*	78(23-143)	30(0-120)	60(10-120)	120(53-180)
MSKSLEDAI = 4	26/36	4/11	14/14	11/11
MSK-BILAG				
A	3/36	0/11	1/14	2/11
B	19/36	3/11	10/14	7/11
C	10/36	5/11	3/14	2/11
D	4/36	3/11	0/14	0/11

DMARD: disease modified anti rheumatic drug, NO: for number of patient, * Median (IQR), SJC: swollen joint count, TJC: tender joint count, EMS: early morning stiffness, BILAG: British Isles lupus assessment group, SLEDAI: systemic lupus erythematosus disease activity index, US: ultrasound, VAS: visual analogue scale.

9.7.1 *MRI scores between groups*

MRI Scores for the three groups are shown in (Figure 9-1). RAMRIS total synovitis score was significantly higher in patients with subclinical synovitis compared to those with normal ultrasound. There was a strong correlation between ultrasound total synovitis and MRI RAMRIS total synovitis scores (R=0.689, p<0.001). The tenosynovitis and bone marrow oedema scores did not significantly differ between groups. This is probably because of small patient numbers and low values for these scores in all groups. The RAMRIS synovitis score did not significantly differ between the subclinical synovitis and clinical synovitis groups.

Figure 9-1: RAMRIS Synovitis Scores according to ultrasound and clinical status

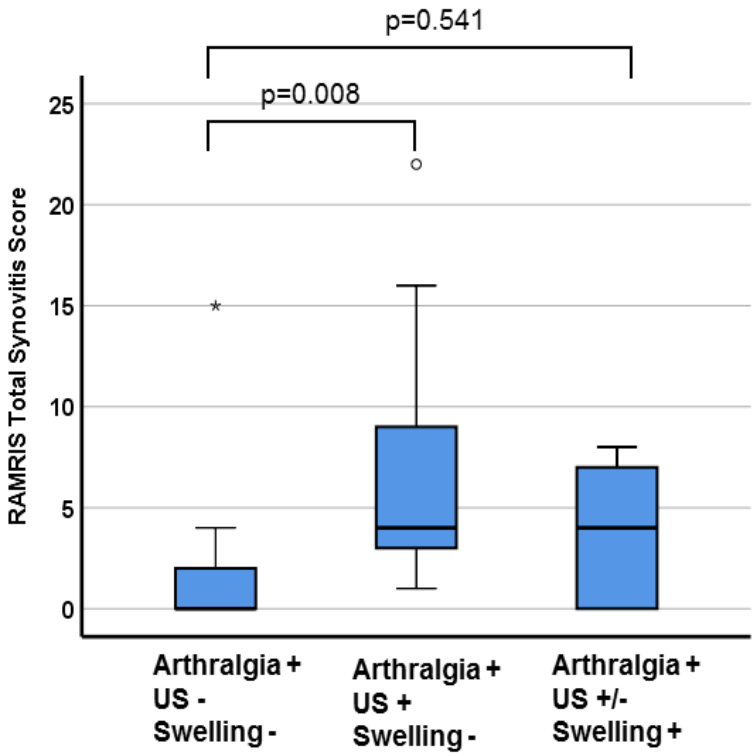


Figure 9-1: The first group is patients with arthralgia and normal ultrasound and absence of clinical synovitis. The second group: patients with arthralgia and Ultrasound only-synovitis. The third group: patients with clinical synovitis +/- abnormal scan (Grey scale >1and or Power Doppler>0 for the joints and Grey scale>0 and or Power Doppler >0 for the tendons)

9.7.2 *Agreement between MRI and ultrasound at each site*

Overall agreement between clinical and ultrasound assessment on joint-by-joint analysis, as measured by Kappa and prevalence-adjusted-bias-adjusted Kappa, was reasonably good and PABAK ranged between 0.37-0.90. (Table 9-2). There were a small number of cases in which ultrasound detected more than MRI, or vice versa. The best agreement was in the MCPs, PIPs and flexor tendons.

Table 9-2: Agreement between ultrasound and MRI

Joints	US criterion	PEA	US<MRI	US>MRI	Sp(-ve)	Sp(+ve)	Kappa (95% CI)	PABAK
RCJ	GS>1 ± PD≥1	80.0% (28/35)	2.9% (1/35)	17.1% (6/35)	80.0% (28/35)	80.0% (28/35)	0.61 (0.61, 0.61)	0.60
ICJ	GS>1 ± PD≥1	82.9% (29/35)	2.9% (1/35)	14.3% (5/35)	85.0% (34/40)	80.0% (24/30)	0.65 (0.65, 0.65)	0.66
UCJ	GS>1 ± PD≥1	71.4% (25/35)	2.9% (1/35)	25.7% (9/35)	78.3% (36/46)	58.3% (14/24)	0.40 (0.40, 0.40)	0.43
MCP2	GS>1 ± PD≥1	77.1% (27/35)	11.4% (4/35)	11.4% (4/35)	81.0% (34/42)	71.4% (20/28)	0.52 (0.52, 0.52)	0.54
MCP3	GS>1 ± PD≥1	68.6% (24/35)	11.4% (4/35)	20.0% (7/35)	76.6% (36/47)	52.2% (12/23)	0.29 (0.29, 0.29)	0.37
MCP4	GS>1 ± PD≥1	85.7% (30/35)	5.7% (2/35)	8.6% (3/35)	91.2% (52/57)	61.5% (8/13)	0.53 (0.53, 0.53)	0.71
MCP5	GS>1 ± PD≥1	85.7% (30/35)	2.9% (1/35)	11.4% (4/35)	91.8% (56/61)	44.4% (4/9)	0.37 (0.37, 0.37)	0.71
PIP2	GS>1 ± PD≥1	77.1% (27/35)	8.6% (3/35)	14.3% (5/35)	85.7% (48/56)	42.9% (6/14)	0.29 (0.29, 0.29)	0.54
PIP3	GS>1 ± PD≥1	94.3% (33/35)	2.9% (1/35)	2.9% (1/35)	96.7% (58/60)	80.0% (8/10)	0.77 (0.77, 0.77)	0.89
PIP4	GS>1 ± PD≥1	85.7% (30/35)	5.7% (2/35)	8.6% (3/35)	92.1% (58/63)	28.6% (2/7)	0.21 (0.21, 0.21)	0.71

Joints	US criterion	PEA	US<MRI	US>MRI	Sp(-ve)	Sp(+ve)	Kappa (95% CI)	PABAK
PIP5	GS>1 ± PD≥1	88.6% (31/35)	5.7% (2/35)	5.7% (2/35)	93.1% (54/58)	66.7% (8/12)	0.60 (0.60, 0.60)	0.77
ECU	GS≥1 ± PD≥1	86.1% (31/36)	8.3% (3/36)	5.6% (2/36)	92.3% (60/65)	28.6% (2/7)	0.21 (0.21, 0.21)	0.72
ETS	GS≥1 ± PD≥1	85.7% (30/35)	14.3% (5/35)	0.0% (0/35)	92.1% (58/63)	28.6% (2/7)	0.25 (0.25, 0.25)	0.71
FT2	GS≥1 ± PD≥1	94.4% (34/36)	5.6% (2/36)	0.0% (0/36)	97.1% (68/70)	0.0% (0/2)	Not calculated	0.89
FT3	GS≥1 ± PD≥1	94.4% (34/36)	5.6% (2/36)	0.0% (0/36)	97.1% (68/70)	0.0% (0/2)	Not calculated	0.89
FT4	GS≥1 ± PD≥1	97.3% (36/37)	2.7% (1/37)	0.0% (0/37)	98.6% (70/71)	66.7% (2/2)	0.65 (0.65, 0.65)	0.90
FT5	GS≥1 ± PD≥1	94.4% (34/36)	5.6% (2/36)	0.0% (0/36)	97.1% (68/70)	0.0% (0/2)	Not calculated	0.89

MRI: magnetic resonance imaging, PEA: Percentage exact agreement; Sp(+ve): proportions of category-specific positive agreement; Sp(-ve): proportions of category-specific negative agreement; PABAK: Prevalence-adjusted bias-adjusted kappa. US: ultrasound

9.7.3 *Qualitative features of musculoskeletal SLE appearances on MRI*

On overall review of the MRI appearances with an experienced musculoskeletal radiologist, a number of qualitative observations about the appearances could be made.

V. MRI synovitis found in wrists more than hand joints

In common with other studies in SLE, synovitis occurred more frequently at the wrist joint (19 patients) than in the other hand joints. Three patients had normal ultrasound, but did have MRI confirmed synovitis, which is a possible explanation for inflammatory pain in the ultrasound-negative group.

VI. Extensor tendons affected more frequently than flexor tendons

Most studies in arthritis that use RAMRIS did not report the extensor tendons. However, in my study I found this was the most common site to be affected, which was also more commonly seen at the wrist. Only one patient had flexor tenosynovitis

VII. Effusions without enhancement

We found some patients who had clinical synovitis at the MCP joints, but the RAMRIS synovitis scores were reported as normal for these patients. On review of the T2 images, it was noted that these patients had joint effusions without synovial enhancement. This may be non-inflammatory, and is therefore a potential weakness of clinical examination. However, there are potential artefactual explanations for this as well. The timing of the injection may be an issue the longer the gap, the more likely synovitis enhances. Also, weight to dosage ratio of contrast injection (the dose was not matching the weight). Six patients with normal ultrasound and no clinical swelling also had this type of effusion.

VIII. Low prevalence of bone marrow oedema and erosions

In RA, bone marrow oedema is frequent and is a precursor to bone erosion, which is an important pathological process in terms of long term prognosis. However, in the SLE patients, bone marrow oedema was negative for all patients in MCP and PIP joints. Bone marrow oedema of the small joints of the hands appears to not to be a feature in SLE. Bone marrow

oedema was seen in the wrist and carpus (intercarpal joint, in five patients) but was mild when it occurred. Erosions occurred in approx. <10% of SLE cases. In the hand and wrist, if they occur, this is predominantly seen in the index, middle finger MCP joints and wrist joints. In my observations, the most common bone affected was the capitate (in 14 patients), followed by the lunate (in 10 patients) then MCP3 (in 7 patients). Although the number of patients with erosions was low, it is notable since these patients are usually considered to have a non-erosive form of arthritis.

IX. Avascular necrosis of the lunate as a potential explanation for pain with normal ultrasound

In one patient, who had both SLE and antiphospholipid syndrome, there was bone marrow oedema of the entire lunate. This is suggestive of avascular necrosis rather than being secondary to inflammatory arthritis. Avascular necrosis is well described at other sites in SLE. Although this particular patient did also have synovitis at other sites, this finding is interesting since it demonstrates a potential non-inflammatory mechanism for pain related to SLE pathology, which would not be detected on clinical examination or on ultrasound.

Figure 9-2: Non-enhancing effusion in an MCP

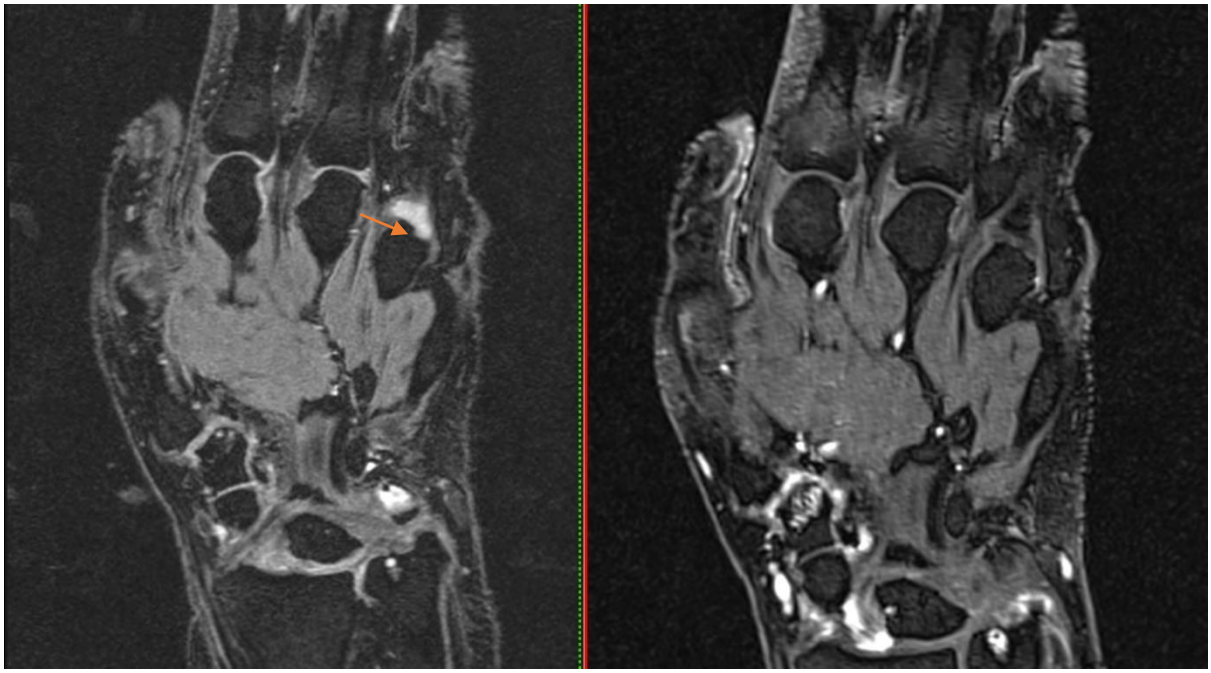


Figure 9-2: Parallel Coronal T2 fat-sat DESS (left) and Coronal T1 fat-sat VIBE post-Gadolinium injection images. Images acquired at the same plane and slice. The coronal T2 fat-sat DESS sequence a large effusion within the ring finger MCP joint. The coronal T1 fat-sat VIBE post-Gadolinium sequences demonstrates no appreciable enhancing synovitis within the ring finger MCP joint.

Figure 9-3: Enhancing synovitis in hand joints

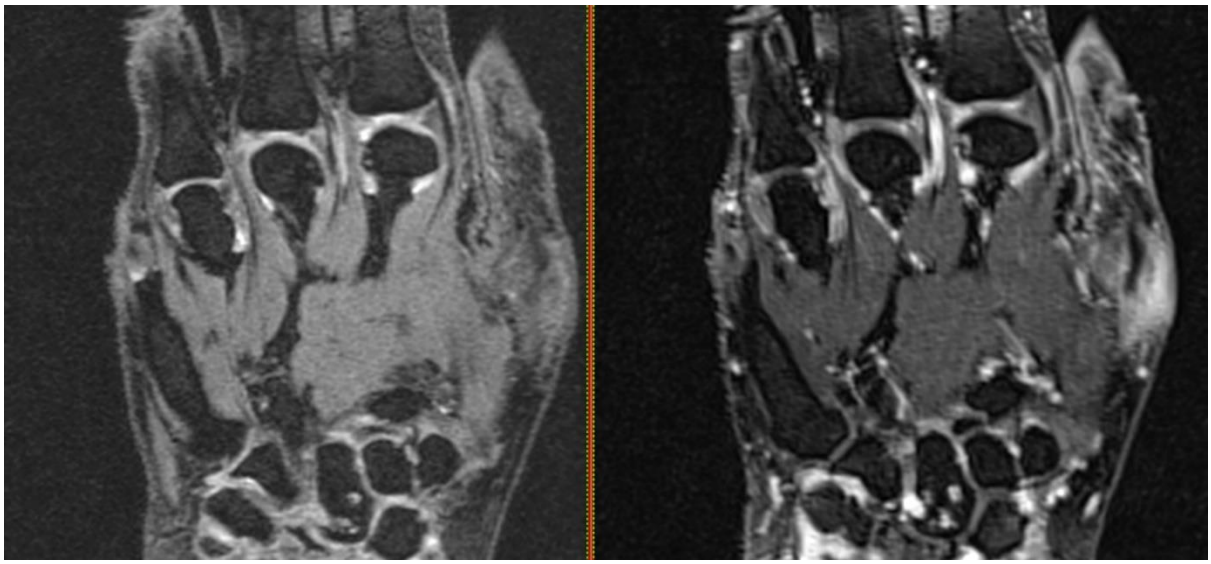


Figure 9-3: Parallel Coronal T2 fat-sat DESS (left) and Coronal T1 fat-sat VIBE post-Gadolinium injection images. Images acquired at the same plane and slice. The coronal T2 fat-sat DESS sequence demonstrates effusions within the index, middle and ring finger MCP joints. The coronal T1 fat-sat VIBE post-Gadolinium sequences demonstrates enhancing synovitis within the index, middle and ring finger MCP joints.

9.8 Discussion:

Although this is an interim analysis, it provides several insights into my ultrasound results. First, MRI was able to validate the ultrasound-only synovitis. This is important because ultrasound is an operator-dependent method and it is possible for an inexperienced sonographer to over-score abnormalities. The agreement with MRI re-assures that the ultrasound results in my other chapters were accurate.

Three other studies have reported MRI synovitis in SLE. Ball and colleagues found synovitis in the MCPs in 27/34 patients and wrist synovitis in 28/34 patients, consistent with the patterns I found[374]. Ostendorf et al.[268, 370] used MRI to assess both hands of 14 patients with SLE and varied arthritis severity and duration. They found active synovitis in 64%, tenosynovitis in 71%, and bone erosion in 57%. Boutry et al. compared patients with RA, SLE, and systemic sclerosis. Synovitis was identified in all SLE patients mainly at the wrists, 2nd, and 3rd MCP joints[371]. The pattern and distribution of joint involvement are different between SLE and RA. In RA, tendon sheath inflammation is commonly seen and the extensor carpi ulnaris tendon appears to be most commonly affected [368, 420].

MRI gives some additional information that is not possible using ultrasound. In particular it gives information about bone oedema and erosion. Bone marrow oedema represents cellular infiltrations in the subchondral bone. Bone marrow oedema has prognostic value in patients with RA [421] this may help in risk stratification and taking decision for early treatment. It has high specificity and higher accuracy for joint damage progression [422].

However, SLE is known to have less tendency for bone erosion than RA. One previous paper has reported bone oedema in SLE patients in 7.5% and 35.5% at hand and wrist respectively[372]. This is markedly higher than I found in my study. It is not clear whether this difference is due to the populations of patients recruited in the imaging protocols and reporting.

In my study, I found that some patients had non-enhancing effusions. This was also shown by Zollers et al. They also found patients with swelling on examination with abnormal T2 images

but no enhancement on MRI [423]. This could explain the cause of pain in patients with normal clinical examination and ultrasound scan.

The main limitation of this study was the small sample size. However, this is a pilot study and could provide an important insight into larger cross-sectional and longitudinal MRI studies. This study did not include control groups such as RA to assess difference in pathology or normal volunteers to validate the frequency and importance of some of the findings. However, that could be incorporated in a future extension to this study. In this study RAMRIS scoring system was used, although this was actually developed to evaluate patients with RA. Although MRI RAMRIS scores are known to be highly objective and reproducible, in SLE arthritis they have not themselves been validated against a gold standard such as synovial biopsy.

9.9 Conclusion

MRI provided further validation for ultrasound assessment of SLE joint disease, it could potentially give additional information about the causes of pain in people with normal ultrasound, and demonstrates some differences in the pattern of synovitis in patients with SLE compared previous reports in RA.

Chapter 10: Discussion

10.1 General discussion of results:

The data presented in this thesis highlighted the importance of understanding SLE arthritis and its impact on the treatment and quality of life.

To summarise the background: musculoskeletal SLE is a significant healthcare problem. Patients report poor quality of life despite the best current therapy and since musculoskeletal disease is so frequent, this has a greater impact on wellbeing at a population level than manifestations that are more severe, but less common. My review of the background literature suggests that this problem is not only due to a lack of useful therapies. Instead, it may be because physicians are not able to reliably identify the active disease that needs treatment and because clinical trials are not able to accurately appraise new treatments.

I therefore developed the themes of my thesis to answer these problems. I focussed on the accurate measurement of musculoskeletal disease activity, particularly using imaging as an objective assessment. This is important because most other outcomes measures in research have not included an objective “gold standard”, instead of correlating instruments with overall physician impression and therapy decisions. Hence, my research was designed not only to understand the value of imaging but, it is also used imaging as a way to understand clinical instruments and clinical trials.

My key findings elucidate: (1) the prevalence of different phenotypes of musculoskeletal disease activity, and therefore which patients should be treated in clinical practice and trials; (2) the responsiveness of different instruments; (3) the pathological explanation for pain based on ultrasound and MRI imaging.

These studies form part of an ongoing programme of musculoskeletal SLE research with the ultimate objective of designing and completing a new type of trial design. This programme is outlined in Figure 10-1.

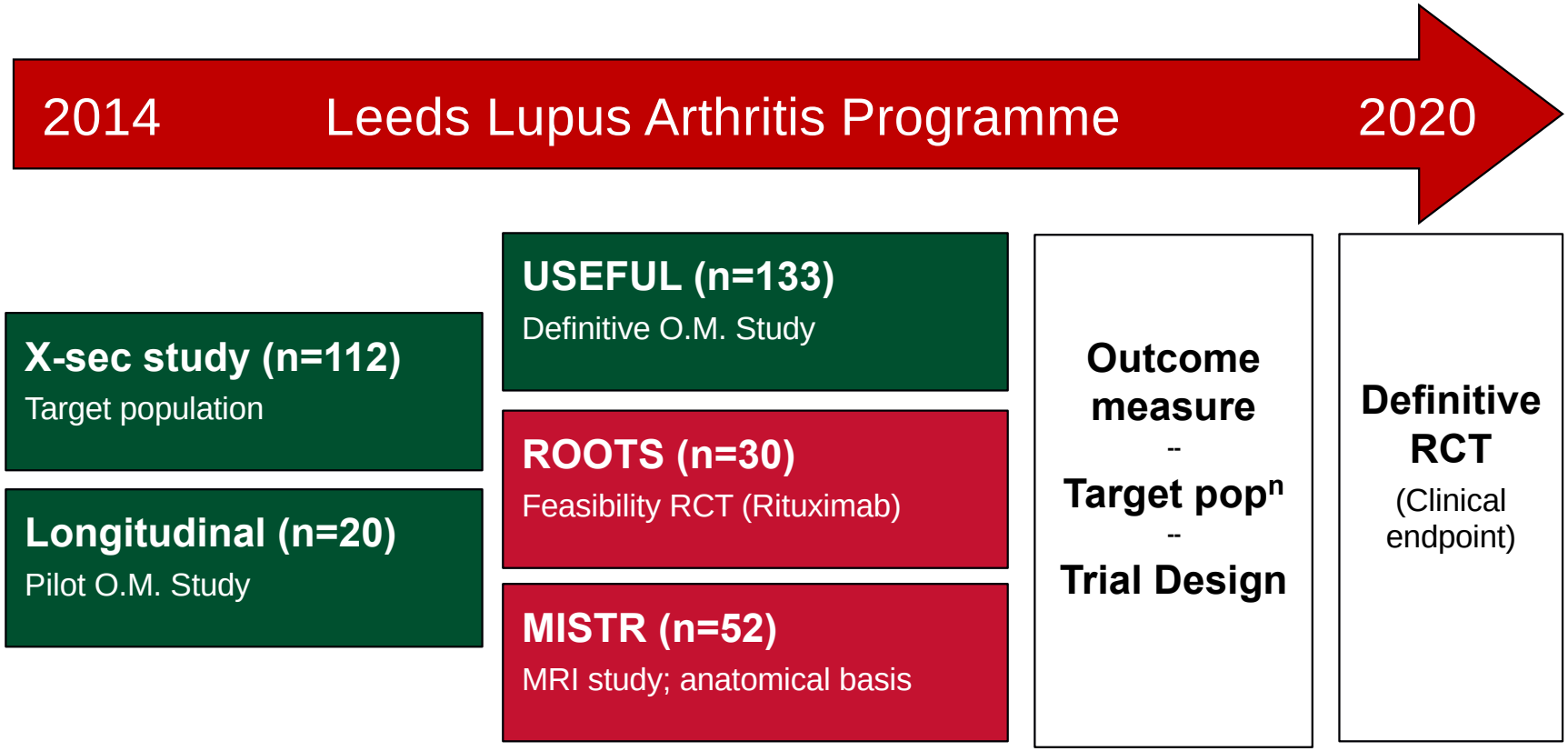


Figure 10-1: Leeds Lupus Arthritis Programme

Studies shown in green are completed as part of my thesis. Studies in red are still in progress (interim MRI results included in thesis, but recruitment continues).

Studies shown in white are planned, based on my results. OM: outcome measure. ROOTS: Rituximab Objective Outcomes Study in SLE

The ultimate product of my thesis will be to define the target population for a clinical trial as well as a new outcome measure (discussed further below). The ROOTS study (Rituximab Objective Outcomes Study in SLE) is a feasibility RCT that has currently recruited 25/30 planned patients. That study will evaluate the new outcome measure in a randomised study using rituximab or placebo. Once ROOTS has been completed and analysed, we will use the results to design a definitive multicentre RCT to test the efficacy of rituximab in musculoskeletal SLE. I will use the results of the USEFUL study in further statistical analysis to define a new continuous outcome measure. I anticipate that the next RCT will use that new clinical outcome measure as the primary endpoint, rather than ultrasound.

10.1.1 *Chapter 5: Cross-sectional study*

Previous ultrasound studies were reviewed in my literature review and also in a previous systematic literature review by my group. This highlighted several key problems with these studies relating to the inclusion criteria, controlling for medications use and excluding rhupus. As a result, there was great uncertainty surrounding the prevalence of different abnormalities and the importance of ultrasound synovitis. Also, the other ultrasound studies did not standardise which joints assessed and use did not always use OMERACT reporting of ultrasound findings. I, therefore, performed a larger, more rigorously designed cross sectional study to define the frequency and clinical associations of ultrasound-only synovitis. My key findings were that 38% of patients had swollen joints (clinical synovitis), 27% had ultrasound-only synovitis, and 34% had no evidence of inflammation. Ultrasound-only synovitis was associated with worse symptoms and serology than patients with normal scan. These results therefore indicate that outcome measures, treatment decisions and trials must account for subclinical synovitis.

10.1.2 *Chapter 6: Pilot longitudinal study*

In my literature review, I reviewed various outcome measures used in trials. It is apparent that both the BILAG and SLEDAI have limitations in responsiveness. Joint counts, VAS and EMS are sometimes reported but have not been well validated. Also, most validation studies are

performed in patients in routine clinical care, with many different types of therapy. In this study I therefore explored the responsiveness of these various instruments using patients with a single type of therapy (Depo-medrone) and included ultrasound as an objective standard. The key finding was that many clinical outcome measures underestimate responsiveness. In particular, patients not achieving an SRI-4 response (as used in most trials) could have a substantial improvement in synovitis. In summary, ultrasound demonstrates the limitations of existing tools, but demonstrates that a better tool could be designed. This would improve a clinical trial. I used the results to design the USEFUL study.

10.1.3 *Chapter 7: predictive value of ultrasound synovitis*

This study follows on from my cross-sectional findings. The results in chapter 5 showed that many patients without joint swelling (and therefore only scoring BILAG C/D or SLEDAI=0 for musculoskeletal) have objective ultrasound synovitis. I therefore asked whether patients should be treated according to baseline ultrasound findings.

There were several important decisions in the design of the study that must be reviewed in light of the results. First, what the outcome measure should be to compare the responses of ultrasound positive and negative patients. We needed a continuous outcome measure, but there were very limited data on whether this should be a tender or swollen joint count, VAS or some other measure. We decided to choose the most responsive outcome measure and time point (see below) in an interim analysis of the first 70 patients. The study was powered based on this statistic. We also had to decide what therapy we would assess. We decided to use glucocorticoids because it was one of the most commonly used therapies, has a fairly predictable efficacy, and works over a short period. Lastly, we had to decide the best time points to measure the effect. In the pilot study we used two weeks and four weeks as these time points should match the effectiveness of glucocorticoids. However, one problem we discovered with this is that it is theoretically not possible for the BILAG and SLEDAI scores to improve fully over this period – they capture all of the past 30 days disease activity and glucocorticoids don't work instantly. For this reason we chose two and six week time points.

Ultimately, our decision was to analyse the EMS VAS at two weeks between the groups of patients who were ultrasound positive and negative baseline.

The primary outcome measure was not met – the groups did not differ in responsiveness according to ultrasound, although there was a trend to better responses with positive ultrasound. However, on reviewing the baseline characteristics and responsiveness data we considered that there may have been some drawbacks to our choices. The most responsive outcome measure may not necessarily be the best – there was more variability in outcomes at six weeks. Also, an outcome measure that is largely patient-reported may be affected by other conditions, such as fibromyalgia. I, therefore, performed post-hoc analyses excluding patients with fibromyalgia at baseline and analysing both two and six week data. In these post-hoc analyses, baseline ultrasound was a statistically significant predictor of response to therapy.

Another potential limitation of this study is that only glucocorticoids were assessed. Glucocorticoids may be effective for many different types of joint pain over a short period, such as osteoarthritis. It would also be valuable to assess ultrasound and outcome measures in patients treated with a more specific SLE therapy. Lastly, the USEFUL study may be affected by observer bias; although the clinical assessor, sonographer and patient were blinded to each other's results, they were not blinded to time point. These limitations are being addressed in the ROOTS study, which is randomised and compares rituximab with placebo.

From this study we can draw several conclusions. First, it seems clear that fibromyalgia may confound the assessment of SLE therapies. Physicians should consider this in their practice, and in clinical trials it may be appropriate to exclude patients with fibromyalgia (without synovitis). Second, although it was a post-hoc analysis, it seems reasonable to conclude that ultrasound can identify patients who will respond to therapy, with the exclusion of fibromyalgia being clinically logical. It is worth noting at this point that I did find that synovitis could be present with or without fibromyalgia. If a patient does have fibromyalgia, then it does not mean that they should not be considered for treatment, and indeed ultrasound may be especially

helpful in this scenario. However, if a patient has fibromyalgia then it is much more difficult to tell whether that treatment has worked on clinical grounds alone.

10.1.4 *Chapter 8: responsiveness of ultrasound and clinical variables*

My pilot longitudinal study already showed that some variables were more responsive than others: ultrasound, physician VAS and BILAG were the most responsive. SLEDAI, joint counts and patient-reported outcome measures were less responsive. However, that study only included patients with objective synovitis – not patients with ultrasound-only synovitis, whom I now believe to be an important group to assess. Also, the pilot study only included 20 patients and collected a more limited set of clinical data.

There were some differences from the earlier study in the responsiveness data from the USEFUL study. The most responsive variables in the USEFUL study (considering only patients with active ultrasound at baseline) were: ultrasound, physician VAS, BILAG, SLEDAI and patient painful joint count, although none of these reached the same levels of responsiveness as in the earlier study. This may be because of the lower degree of clinical synovitis in the USEFUL study, or because of the six week time point, when the effects of Depo-medrone may be reducing.

The results were less clear when it came to comparing ultrasound responses to patient Likert responses. The correlation between these variables was poor. Although this was the protocol-specified analysis, I believe that in future research responsiveness should be validated against other longer term outcomes instead of patient-reported improvement.

10.1.5 *Chapter 9: MRI validation*

My MRI study is not completed yet, but I presented an interim analysis. The key purpose of this study was to validate ultrasound-only synovitis. In other words, to confirm that it is “real” using another method. This was achieved: patients with ultrasound-only synovitis had higher MRI scores for synovitis, assessed by a radiologist who was blinded to the ultrasound results. There were several other interesting observations. I was interested in why some patients

whose pain sounded inflammatory (e.g. they had symmetrical small joint involvement and morning stiffness) had surprisingly normal ultrasound. In MISTER, a small number of patients had MRI synovitis which was not detected by the ultrasound, which may help explain why some SLE patients have pain. Also, one patient had avascular necrosis that is another explanation for pain not seen on ultrasound. Meanwhile, some MCP joints had non-enhancing effusions that may be reported as joint swelling but are not truly inflammatory.

10.1.6 *Recent research by other groups*

Following the completion of my full time research, another group published a new disease activity tool: the SLEDAS, based on the SLEDAI but with different weightings for the individual items. For the musculoskeletal domain, the investigators included a term for the swollen joint count. I therefore assessed this instrument in my pilot longitudinal population (in press). I found that it was more responsive than the SLEDAI, but not as responsive as the BILAG, physician VAS and ultrasound. Therefore I remain confident that a better outcome measure can be designed for musculoskeletal SLE.

10.2 Impact of research:

This programme of research is of importance both nationally and globally in improving understanding of SLE arthritis and how to monitor it. Based on my results, physicians will be able to use ultrasound in their clinics to make treatment decisions and more patients with ultrasound-only synovitis will receive effective therapy. The most important longer term outcomes will derive from the use of my results in the design of clinical trials.

10.3 Future prospective:

Following my planned PhD projects I will use the results of the USEFUL and other studies to design a new clinical outcome measure. Statistical analysis for this is in progress but it appears that a composite tool derived from variables such as the swollen joint count, physician VAS for musculoskeletal disease activity, patient VAS for musculoskeletal pain and ESR can be combined to create a tool that correlates better with ultrasound-confirmed synovitis and is

more responsive than existing tools. The other advantage of this tool may be that it is easier to standardise between assessors with differing expertise. Also, as a continuous variable, it is statistically more powerful, so that smaller numbers of patients are needed in an RCT.

The ROOTS study will capture the data needed to calculate this tool. Therefore at the end of the ROOTS study I will have the data needed to define the eligibility criteria for a study (clinical or ultrasound synovitis, no fibromyalgia), and the primary outcome measures, as well as a standard of care that does not include medium or high doses of glucocorticoids.

I will therefore be able to design a more effective trial in SLE arthritis and provide new proven therapies to patients.

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Chapter 12: Appendices

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RE. Ahmed S Zayat et al. Defining inflammatory musculoskeletal manifestations in systematic lupus erythematosus. *Rheumatology* (2019) 58 (2): 304-312, doi: 10.1093/rheumatology/key277

Khaled Mahmoud et al. Responsiveness of clinical and ultrasound outcome measures in musculoskeletal systematic lupus erythematosus. *Rheumatology* (2019), doi: 10.1093/rheumatology/key422

Thank you for your email. I can confirm that the second article titled '**Responsiveness of clinical and ultrasound outcome measures in musculoskeletal systematic lupus erythematosus**' is published under a **CC-BY-NC** license which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. As a result, you may share and distribute this article on non-commercial websites and repositories immediately upon publication.

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CONSENT FORM

Title of Project: Leeds Teaching Hospitals Connective Tissue Disease Cohort Cross-sectional and Longitudinal Clinical and Basic Science Evaluation (CONVAS): Imaging and Biological Sub-study

SUBJECT INITIALS ☐☐☐ SUBJECT NO. ☐ SUBJECT DOB ☐☐☐

Name of Researcher:.....

Please initial boxes

1. I confirm that I have read and understand the information sheet dated 2nd November 2012 version 1.0 for the above study, that I have had the opportunity to ask questions and that I have received satisfactory answers to the questions that I have asked. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that sections of any of my medical notes may be looked at by responsible individuals from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐

4. I understand that even if I withdraw from the clinical study, the data and samples collected from me will be used in analysing the results of the study. I understand that my identity will remain anonymous. ☐

5. I agree for the results from this study to be submitted to the Rheumatology department BioBank and for this to be updated from my medical and electronic records in order to support additional research activities. ☐

6. I agree to my GP being informed regarding my participation in this study ☐

7. I agree that any samples that are not used at the end of the study will be transferred to a Research Tissue Bank and will be used in future studies within this research area. ☐

8. I agree to have genetic tests done on samples for research purposes. ☐

Name of Patient Date Signature
(Please print your name and date your own signature)

Name of Person taking consent Date Signature
(Investigator/delegated medically – qualified sub investigator)

Original copy – site file
1 copy for patient
1 copy to be kept with hospital notes
1 copy to be kept with hospital notes

NHS
Health Research Authority

Dr Edward Marc John Vital
Associate Professor and Honorary Consultant NIHR Clinician Scientist
University Of Leeds
2nd Floor, Chapel Allerton Hospital
Chapeltown
LS7 4SA

Email: hra.approval@nhs.net

11 March 2016

Dear Dr Vital

Letter of HRA Approval

Study title:	**A prospective observational study to investigate the validity of ultrasound as an outcome measure in assessing response to therapy in Systemic lupus erythematosus (SLE)**
IRAS project ID:	**186251**
Protocol number:	**RR16/005**
REC reference:	**16/NW/0060**
REC favourable opinion with conditions	**07 March 2016**
Sponsor	**University of Leeds**

I am pleased to confirm that the above study has been given HRA Approval, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

Scope

HRA Approval provides an approval for research involving NHS patients or staff in England. Organisations listed in your application are not obliged to undertake this study; arrangements for organisations to confirm their capacity and capability to undertake the study, where formal confirmation is required, are detailed in *Appendix B Summary of HRA assessment* (*Participating NHS Organisations*, *Capacity and Capability* and *Agreement* sections).

If your study involves participating organisations in other countries in the UK, please contact the relevant national coordinating functions for support and advice. Further information can be found at http://www.hra.nhs.uk/resources/applying-for-reviews/nhs-hsc-rd-review/.

If there are participating non-NHS organisations, local agreement should be obtained in accordance with the procedures of the local participating non-NHS organisation.

Participating NHS Organisations in England

The sponsor and each participating NHS organisation in England should work jointly to assess, arrange and confirm that the participating organisation has the capacity and capability to undertake its role in this research. Further details about what this should entail are described in *Appendix B - Summary of HRA assessment*.

The sponsor should work with other participating NHS organisations in England to assess, arrange and confirm that the participating organisation has the capacity and capability to undertake its role within this research. Further details about this are given in *Appendix B - Summary of HRA assessment*.

It is critical that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. This is the case even where some or all participating NHS organisations in England are not required to provide formal confirmation of capacity and capability, as the HRA expects the organisations' research management functions to confirm by email to the CI and sponsor that the research may proceed in advance of the no-objection deadline (where one is given). Contact details and further information about working with the research management function for each organisation can be accessed from http://www.hra.nhs.uk/hra-approval.

For guidance on how you and the sponsor should work with participating NHS organisations in England, please see *Appendix B* (*Participating NHS Organisations, Capacity and Capability* and *Agreement* sections).

After HRA Approval

The document *"After Ethical Review – guidance for sponsors and investigators"*, issued with your REC favourable opinion (or favourable opinion with conditions), gives detailed guidance on reporting requirements for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting requirements or procedures.

In addition to the guidance in the above, please note the following:

HRA Approval applies for the duration of your REC favourable opinion, unless otherwise notified in writing by the HRA.

Substantial amendments should be submitted to the Research Ethics Committee, as detailed in the *After Ethical Review* document. However, amendments to this study that are not substantial amendments ("minor amendments") should be submitted for review by the HRA using the form provided on the HRA website, and emailed to hra.approval@nhs.net.

IRAS project ID	186251

The HRA will categorise amendments to clarify whether participating NHS organisations in England are required to formally confirm that they have the capacity and capability to implement the amendment prior to implementation. Further details can be found on the HRA website.

New Participating Organisations

Plans to include any new participating organisations in the study in addition to those listed in the application should be notified to the HRA as an amendment. The study should not start at the new participating organisation until:

- For Clinical Trials of Investigational Medicinal Products (CTIMPS), the HRA has acknowledged that the amendment has been received by the Research Ethics Service.
- For NHS organisations in England, the organisation has confirmed capacity and capability, where required to do so, in line with the guidance provided by the HRA in the HRA categorisation email for the amendment.
- For NHS organisations in Northern Ireland, Scotland or Wales, management permission has been obtained.
- For non-NHS organisations, management permission has been obtained and SSA has been obtained from the REC where necessary.

Appendices

The HRA Approval letter contains the following appendices:

- A – List of Documents reviewed during HRA assessment
- B – Summary of HRA Assessment

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 email the HRA at hra.approval@nhs.net. Additionally, one of our staff would be happy to call and discuss your experience of HRA Approval.

HRA Training

We are pleased to welcome researchers and research management staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

Your IRAS project ID is **186251**. Please quote this on all correspondence.

Yours sincerely

Sharon Northey
Senior Assessor

Email: hra.approval@nhs.net

NHS
Health Research Authority

North West - Greater Manchester Central Research Ethics Committee
3rd Floor
Barlow House
4 Minshull Street
Manchester
M1 3DZ

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 March 2016

Dr Edward Marc John Vital
Associate Professor and Honorary Consultant NIHR Clinician Scientist
University Of Leeds
2nd Floor, Chapel Allerton Hospital
Chapeltown
LS7 4SA

Dear Dr Vital

Study title:	**A prospective observational study to investigate the validity of ultrasound as an outcome measure in assessing response to therapy in Systemic lupus erythematosus (SLE)**
REC reference:	**16/NW/0060**
Protocol number:	**RR16/005**
IRAS project ID:	**186251**

Thank you for your letter of 29th March 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, Kath Osborne, nrescommittee.northwest-gmcentral@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.

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 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" below).

Non-NHS sites

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Contract/Study Agreement [mNCA]		20 January 2016
Contract/Study Agreement [Material Transfer Agreement]		20 January 2016
Covering letter on headed paper [Response letter]		25 February 2016
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [University of Leeds Indemnity certificate]	1.0	22 September 2015
GP/consultant information sheets or letters [GP letter]	1.0	02 December 2015
GP/consultant information sheets or letters [GP letter]	2.0	23 February 2016
IRAS Application Form [IRAS_Form_29022016]		29 February 2016
IRAS Application Form XML file [IRAS_Form_29022016]		29 February 2016
IRAS Checklist XML [Checklist_29022016]		29 February 2016
Other [Sponsorship letter]	1.0	06 January 2016
Participant consent form [Consent form]	1.0	08 December 2015
Participant consent form [Consent form_clean]	2.0	19 February 2016
Participant information sheet (PIS) [Patient Information Sheet_tracked]	2.0	19 February 2016
Participant information sheet (PIS) [Patient information sheet_clean]	2.0	19 February 2016
Research protocol or project proposal [Study Protocol_cleaned]	2.0	23 February 2016
Summary CV for Chief Investigator (CI) [CV of CI]	1.0	01 February 2014

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/

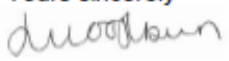
HRA Training

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/NW/0060	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely



On behalf of
Professor S J Mitchell
Chair

Email:nrescommittee.northwest-gmcentral@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Ms Anne Gowing, Leeds Teaching Hospitals NHS Trust*

Leeds (East) Research Ethics Committee
Yorkshire and Humber REC Office
First Floor, Millside
Mill Pond Lane
Meanwood
Leeds
LS6 4RA

Telephone: 0113 3050108

Dr Maya Buch
Department of Rheumatology
Chapel Allerton Hospital
Chapel Allerton
Leeds
LS74SA

15 February 2011

Re-issued 17 June 2011

Dear Dr Buch

Study Title:	**Leeds Teaching Hospitals Connective Tissue Disease and Vasculitis Cohort Cross-sectional and Longitudinal Clinical & Basic Science Evaluation (CONVAS)**
REC reference number:	**10/H1306/88**
Protocol number:	**RR10/9608**

Thank you for your letter of 21 January 2011, 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.

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.

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" below).

The Committee has not yet been notified of the outcome of 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. I will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at non-NHS sites.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of

the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

For NHS research sites only, management permission for research ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where the only involvement of the NHS organisation is as a Participant Identification Centre (PIC), management permission for research is not required but the R&D office should be notified of the study and agree to the organisation's involvement. Guidance on procedures for PICs is available in IRAS. Further advice should be sought from the R&D office where necessary.

Sponsors are not required to notify the Committee of approvals from host organisations.

1. **Change the reference to the document versions in the two consent forms.**

2. **These need to be changed to Version 1.1 17th January 2011 - both at top of page and in the first question**

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).

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Protocol	1.0	19 September 2010
Letter of invitation to participant	1	15 November 2010
GP/Consultant Information Sheets	1.0	15 November 2010
GP/Consultant Information Sheets	1.0	15 November 2010
GP/Consultant Information Sheets	1.0	15 November 2010
Response to Request for Further Information		21 January 2011
Participant Information Sheet: Cardiovasc Sub-Study	1.0	24 September 2010
Participant Information Sheet: & consent form - CONVAS Cardiovasc sub study	1.1	17 January 2011
REC application		
Participant Consent Form: Attached to Patient Information Sheet-SSc Sub-Study	1.0	24 September 2010
Participant Consent Form: Attached to Patient Information Sheet-SSc Volunteer Sub-Study	1.0	11 October 2010
REC Letter		17 December 2010
Participant Information Sheet: Main study	1.0	24 September 2010
Participant Information Sheet: & consent form - CONVAS Main Study	1.1	17 January 2011

Evidence of insurance or indemnity		29 September 2010
Covering Letter		
Investigator CV		20 August 2008
Participant Information Sheet: SSc Sub-Study	1.0	24 September 2010
Participant Information Sheet: SSc Volunteer Sub-Study	1.0	11 October 2010
Participant Information Sheet: Cardiovasc Volunteer Sub-Study	1.0	11 October 2010
Participant Consent Form: Attached to Patient Information Sheet-Main Study	1.0	24 September 2010
Participant Consent Form: Attached to Patient Information Sheet-Cardiovasc Sub-Study	1.0	24 September 2010
Participant Consent Form: Attached to Patient Information Sheet-Cardiovasc Volunteer Sub-Study	1.0	11 October 2010

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

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 website.

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
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

10/H1306/88	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

Dr Carol Chu
Chair

Patient initials: _____ Study Number: _____ Date: __/__/____

USEFUL

Ultrasound scoring sheet

	Right				Left			
	GS	PD	Erosion	Osteophyte X	GS	PD	Erosions	Osteophyte X
RCJ								
ICJ								
UCJ								
ECU								
ETS								
MCP2								
MCP3								
MCP4								
MCP5								
PIP2								
PIP3								
PIP4								
PIP5								
FT2								
FT3								
FT4								
FT5								
Note								

RCJ: Radio carpal joint, ICJ: inter carpal joint, UCJ: Ulnar carpal joint, ECU: Extensor carpi ulnaris, ETS: Extensor tendons sheath, FT: Flexor tendons, MCP: metacarpo-phalangeal joints, PIP: proximal inter-phalangeal joint

12.1 Modified RAMRIS Score sheet

Each of the following structures was scored, giving a maximum possible score of 123

Characteristics		**Score**			
BMO	**Total:51**	0	1	2	3
Region					
MCP2					
MCP3					
MCP4					
MCP5					
PIP2					
PIP3					
PIP4					
PIP5					
RCJ					
ICJ					
Base of Metacarpal 2					
Base of Metacarpal 3					
Base of Metacarpal 4					
Base of Metacarpal 5					
Trapizium					
Trapezoid					
Capitate					

Characteristics		**Score**			
Region					
Hamate					
Scaphoid					
Lunate					
Triquetrum					
Pisiform					
Distal radius					
Distal ulna					
Eosin	**Total:51**	0	1	2	3
MCP2					
MCP3					
MCP4					
MCP5					
PIP2					
PIP3					
PIP4					
PIP5					
RCJ					
ICJ					
Base of Metacarpal 2					
Base of Metacarpal 3					
Base of Metacarpal 4					
Base of Metacarpal 5					

Characteristics		**Score**			
Region					
Trapezium					
Trapezoid					
Capitate					
Hamate					
Scaphoid					
Lunate					
Triquetrum					
Pisiform					
Distal radius					
Distal ulna					
Synovitis	**Total: 33**	0	1	2	3
Region					
RCJ					
ICJ					
UCJ					
MCP2					
MCP3					
MCP4					
MCP5					
PIP2					
PIP3					
PIP4					

Characteristics		**Score**			
PIP5					
Tenosynovitis	**Total:39**				
Region					
Flexor S/P 2nd finger					
Flexor S/P 3rd finger					
Flexor S/P 4nd finger					
Flexor S/P 5th finger					
Abductor pollicis longus/extensor pollicis brevis					
Extensor carpi radialis longus and brevis					
Extensor pollicis longus					
Extensores digitorum and indicis					
Extensor digiti minimi					
Extensor carpi ulnaris					
Flexor carpi radialis					
Flexores digitorum superficialis and profundus					
Flexor pollicis longus					