3 TESLA MAGNETIC RESONANCE IMAGING AND COMPUTERISED IMAGE ANALYSIS IN THE EVALUATION OF RHEUMATOID HAND JOINTS

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Thesis submitted for MD (Res) degree

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This thesis consists of my work except where indicated in the text. All collaborative work is acknowledged where it is described in the thesis. The work was undertaken at Kennedy Institute of Rheumatology, Imperial College London and Robert Steiner MRI Unit, Hammersmith Hospital.

Preliminary work and development of the patient positioning device was done in collaboration with project physicist, Lada V Krasnosselskaia and supervisor Professor Joseph V Hajnal.

Initial image analysis work was carried out in collaboration with staff at IXICO, Ltd, London, primarily Kelvin Leung and Christopher Foley. Algorithms for image analysis conducted at Robert Steiner MRI Unit, were written by physicist, Rita Nunes, under supervision of Professor Joseph V Hajnal.

Digital radiograph analysis using dxr-online™ was performed by SECTRA, Sweden.

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Summary

The work presented in this thesis was aimed at evaluating computerised analysis tools for Magnetic Resonance Imaging (MRI) and radiographic rheumatoid arthritis (RA) disease activity measures longitudinally over time, while imaging at short and long time intervals on a high field strength (3 Tesla) MRI. The work has been presented as preliminary and main studies. The preliminary work was about development of a patient positioning device ‘the bridge’ for wrist imaging, which was subsequently used in a yearlong longitudinal study of RA patients. While imaging patients hand and wrist, the bridge positioning device allowed patients, in a supine position, to position their hands over their abdomen with comfort and good quality reproducible image capture. The main study was a longitudinal observational study of RA patients on routine treatment and healthy subjects using 3T wrist MRI, hand and feet radiographs and analysis using exploratory and new computerised methods in various pilot sub-studies. Techniques that were assessed during pilot work included bone segmentation methods both manual and semi-automatic, with a view to speed up analysis, quantify volume and change in bone shape over time. The registration and transformation technique allowed visual evaluation of small changes over time. The pilot work using computerised digital X-ray radiogrammetric analysis identified correlations between early metacarpal rate of bone mineral density loss with bone marrow oedema change at 1 year, which is a known predictor of future erosions and generated hypothesis that this may represent an earlier disease activity measure. The pilot work using computerised dynamic contrast enhanced MRI (DCE-MRI) analysis highlighted that the dynamic parameters obtained correlate well with semiquantitative synovitis scores, and allow for robust and
sensitive analysis. The reliability of these measures paves way for utilization of this technique in assessment of therapeutic interventions and for remission targets.

Abstract

**Objective:** To explore development and testing of a new patient positioning device during wrist MRI. To evaluate rheumatoid arthritis (RA) wrist 3T MRI with computerised image analysis tools including bone segmentation techniques, semiquantitative scoring and dynamic contrast enhanced (DCE-MRI) for synovitis measures, with similar assessments on healthy subjects. To examine the relationship between X-ray/MRI disease activity measures and bone mineral density loss using computerised digital X-ray radiogammetry (DXR).

**Methods:** Preliminary study was about development and evaluation of a new patient positioning device for wrist imaging and its evaluation against current standard positions. In the main longitudinal MRI study, 13 RA and 10 healthy subjects (HV) were recruited with 10 RA and 7 HV completing the study. Hand/wrist MRI and radiographs were performed over a year and assessed using semi-quantitative scoring and exploratory computerised image analysis tools, which included pilot work on bone segmentation techniques, including manual and semi-automated methods; bone mineral density loss assessment using DXR-online and its comparison with MRI disease activity measures; and dynamic contrast enhanced MRI (DCE-MRI) analysis using Dynamika software.

**Result:** A developed bridge patient positioning device allowed for comfortable, good quality and reproducible imaging as compared to standard positions (Bridge vs hand by the side vs hand above head position: comfort score (out of 10) (mean±std) – 7.3±0.7 vs 7.1±0.8 vs 6.1±1.6, and image quality (Signal to noise/contrast to noise ratio) – 6.1±1.7/3.1±0.5 vs
5.3±1.5/2.6±0.5 vs 7.7±1.1/4±0.5), with subsequent use in a longitudinal study (Comfort score: RA/HV:9.1/8.1). The semi-automated bone segmentation method was much quicker than manual technique (10/8 vs 165/132 minutes for two readers), with good inter and intra-observer similarity for manual method and in between the two methods, though the semi-automated method failed in an advanced RA patient. The manual segmentation using SliceOmatic software was also time consuming - 3256 minutes for 2196 slices, but with image registration and transformation a visual analysis of future images was possible.

In the main longitudinal study, there were stable moderate DAS 28 disease activity scores (Day 1 – 3.9 and week 52 – 4.0). MRI disease activity measures showed good correlation. Bone marrow oedema (BME) correlated with erosions, and automated early 3 month rate of metacarpal digital x-ray radiogrammetric bone mineral density loss (RC-BMD) correlated with 1 year wrist BME change (p=0.035). No significant change was seen for MRI, radiographic or any disease activity measure over the year, though there was small increase in MRI erosion: 2.4 (1.6%), BME: 0.4 (0.8%) and radiographic: 1.8 (0.4%) mean scores. In HV, no radiographic erosions were seen, but MRI showed erosion-like changes, low grade BME and low-moderate synovial enhancement. It was also demonstrated that dynamic contrast enhancement does occur in healthy volunteers, and the inherent variability of perfusion measures obtained with the quantitative DCE-MRI method was small both in HV and stable RA patients on routine treatment.

**Conclusion:** A new MRI wrist patient positioning device was developed, tested and successfully used in a longitudinal study. New and exploratory computerised image analysis techniques in RA, including bone segmentation, DXR and DCE-MRI have a potential role in longitudinal RA clinical trials.
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<tr>
<td>3D</td>
<td>3 Dimensional</td>
</tr>
<tr>
<td>3T</td>
<td>3 Tesla</td>
</tr>
<tr>
<td>ACR</td>
<td>American College of Rheumatology</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis Of Variance</td>
</tr>
<tr>
<td>anti-CCP</td>
<td>Anti-Cyclic Citrullinated Peptide</td>
</tr>
<tr>
<td>ASL</td>
<td>Arterial Spin Labelling</td>
</tr>
<tr>
<td>BMD</td>
<td>Bone Mineral Density</td>
</tr>
<tr>
<td>BME</td>
<td>Bone Marrow Oedema</td>
</tr>
<tr>
<td>CNR</td>
<td>Contrast to Noise Ratio</td>
</tr>
<tr>
<td>COMP</td>
<td>Cartilage Oligomeric Matrix Protein</td>
</tr>
<tr>
<td>CRP</td>
<td>C - Reactive protein</td>
</tr>
<tr>
<td>CT</td>
<td>Computerised Tomography</td>
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<tr>
<td>DAS</td>
<td>Disease Activity Score</td>
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<tr>
<td>DCE</td>
<td>Dynamic Contrast Enhanced</td>
</tr>
<tr>
<td>DCE-MRI</td>
<td>Dynamic Contrast Enhanced Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>DEXA</td>
<td>Dual Energy X-ray Absorptiometry</td>
</tr>
<tr>
<td>DMARDS</td>
<td>Disease Modifying Anti-Rheumatic Drugs</td>
</tr>
<tr>
<td>DTI</td>
<td>Diffusion Tensor Imaging</td>
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<tr>
<td>DWI</td>
<td>Diffusion Weighted Imaging</td>
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<tr>
<td>DXA</td>
<td>Digital X-ray Absorptiometry</td>
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<td>DXR</td>
<td>Digital X-Ray Radiogrammetry</td>
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<td>DXR-BMD</td>
<td>Digital X-Ray Radiogrammetric – Bone Density Mineral Density</td>
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<tr>
<td>eGFR</td>
<td>Estimated Glomerular Filtration Rate</td>
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<tr>
<td>EMS</td>
<td>Early Morning Stiffness</td>
</tr>
<tr>
<td>ESR</td>
<td>Erythrocyte Sedimentation Rate</td>
</tr>
<tr>
<td>EULAR</td>
<td>European League Against Rheumatism</td>
</tr>
<tr>
<td>FA</td>
<td>Flip Angle</td>
</tr>
<tr>
<td>FBC</td>
<td>Full Blood Count</td>
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FFE: Fast Field Echo
FOV: Field of View
Gd: Gadolinium
GSK: GlaxoSmithKline
HAQ: Health Assessment Questionnaire
HAQ DI: Health Activity Questionnaire Disability Index
HLA: Human Leucocyte Antigen
HLA-DR4: Human Leucocyte Antigen DR4 Serogroup
HV: Healthy Volunteers
ICC: Interclass Correlation Coefficient
IL: Interleukin
IP: Interphalangeal
IRE: Initial Rate of Enhancement
JSN: Joint Space Narrowing
MAF: Multi-Assessment Fatigue
MCP: Metacarpophalangeal
MDC: Minimal Detectable Change
ME: Maximum Enhancement
MMP: Matrix Metalloproteinase
MRI: Magnetic Resonance Imaging
MTP: Metatarsophalangeal
NMV: Net Magnetization Vector
OMERACT: Outcome Measures in Rheumatoid Arthritis Clinical Trials
OPG: Osteoprotegerin
OR: Odds Ratio
PACS: Picture Archiving and Communication System
PAD-4: Peptidyl Arginine Deiminase-4
PDUS: Power Doppler Ultrasound
PIP: Proximal Interphalangeal
pQCT: Peripheral Quantitative Computed Tomography
RA: Rheumatoid Arthritis
RANKL: Receptor Activator of Nuclear Factor Kappa-B Ligand
RAMRIS: Rheumatoid Arthritis Magnetic Resonance Imaging Scores
RC: Rate of Change
RE: Rate of Enhancement
REE: Rate of Early Enhancement
RF: Radio Frequency
ROI: Region of Interest
ROC: Receiver Operating Characteristics
SI: Standard Unit
SJC: Swollen Joint Count
SNR: Signal to Noise Ratio
STIR: Short T1 Inversion Recovery
T: Tesla
T1w: T1 weighted
T2w: T2 weighted
TE: Echo Time
TJC: Tender Joint Count
TNF: Tumour Necrosis Factor
TR: Repetition Time
TSE: Turbo Spin Echo
U&E: Urea and Electrolytes
US: Ultrasound
VAS: Visual Analogue Score
vdH Sharp: Van der Heijde modified Sharp Score
1 INTRODUCTION
1.1 Background:

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune multi-systemic disease of unknown origin (1), which leads to permanent disability and unemployment in the majority of patients (2). It can result in significant morbidity, mortality (3-8) and economic burden (9). It is characterised by systemic and articular inflammation associated with progressive polyarticular destruction (10, 11).

RA is the most common form of inflammatory arthritis (12, 13). Its population prevalence is 0.5%-1%, with a highly variable annual incidence (5). The occurrence of RA varies amongst countries and different parts of the world (14). The prevalence in the UK is about 0.4 million affected by the disease (15), with an incidence of 30.8/100,000 for women and 12.7/100,000 for men (16). Its occurrence is two to three times more often in women than in men and has a peak age of onset between 45 to 65 years.

RA typically affects small joints in the hands and feet in a symmetrical pattern (1), causing joint pains, stiffness, swelling and loss of function. Patients can also present with symptoms of fatigue, occasional fevers and a general sense of being unwell. Synovial inflammation forms the hallmark of the disease, resulting in cartilage destruction, bone erosion and joint deformity (1) and future functional disability (11).

The effect on RA is not only limited to synovial joints but can also involve extra-articular organs, leading to a multi-systemic disease. Some of the extra-articular organs involved...
include lungs, skin, blood vessels, heart, nervous system and muscles. The onset of the disease is usually insidious, with a slow onset over weeks to months (12, 17). The diagnosis of RA requires a spectrum of disease manifestations and fulfilment of the conditions as outlined by the American College of Rheumatology (ACR) modified criteria of 1987 (18), and more recently the 2010 ACR-EULAR criteria (19). The regular assessment of the disease involves physicians’ clinical assessments, biochemical markers, subjects’ own assessment and imaging.

1.2 Pathophysiology of RA Joint Damage:

In RA the site of joint based disease pathology is the synovium (20) with tendon sheaths also being involved. The normal synovium is thin and an important source of nutrients. It also synthesises joint lubricants such as hyaluronic acid and collagens that form the synovial interstitium. The synovial fluid is a dialysate of plasma and contains neutrophils and phagocytes (20). In RA, the synovium hypertrophies with infiltration by inflammatory cells, including macrophages, T and B cell lymphocytes, mast and mononuclear cells (21). This inflammatory cellular infiltration and cytokine production, results in synovitis, synovial hyperplasia and angiogenesis. The synovial mass is called a pannus, which is a highly cellular inflammatory tissue (22, 23). Synovial hyperplasia and formation of pannus is the fundamental factor in pathogenesis of RA joint disease. The pannus erodes cartilage and bone by secretion of degrading enzymes like metalloproteinase’s and inflammatory cytokines, for example, tumor necrosis factor α (TNF-α), interleukin 1 (IL-1) and interleukin 6 (IL-6) (10, 20, 23, 24).
Joint cartilage is composed on proteoglycans and type II collagen. In RA, its structural integrity is impaired due to proteolytic enzymes produced from synovium and chondrocytes. Cytokines drive chondrocyte catabolic pathways and matrix destruction resulting in damage. In bone the process of destruction is driven by osteoclasts which differentiate under the influence of inflammatory cytokines.

In RA, genetic associations have been described with HLA alleles (25-29). Other genetic susceptibilities described include protein arginine deiminase-4 (PAD-4) which may lead to increased citrullination (21, 30). The detection of antibodies against cyclic Citrullinated peptides (anti-CCP antibodies) in blood is now a routine test in RA biochemical assessment (31, 32).

Other triggers and associations with RA, have been described with cigarette smoking (33-37), bacterial and viral infections, especially oral periodontal disease (38-40). Propagation of the disease is facilitated by activation of T and B cell lymphocytes. Upon exposure to antigen the T cell gets activated, and produce inflammatory cytokines including IL-12 (21). B cells get activated via cytokines and interactions with T cells and have a role in cytokine production, and antibody forming plasma cells. RA is characterised by presence of autoantibodies, namely rheumatoid factor and anti-CCP. Most of the damage in RA is done by macrophages, fibroblasts and inflammatory mediators. These inflammatory mediators activate synovial fibroblasts, chondrocytes and osteoclasts to result in cartilage and osseous damage (21). Hence, the extent of joint damage and the long term outcome is dependent of this process.
The continued process results in joint destruction and ankylosis (41, 42). Joint damage results in loss of function and physical disability. In the course of the disease, adjacent structures such as bones, tendons, capsule and ligaments are usually involved. In the majority of RA patients, hand and wrists involvement is commonly seen and reflects the patient’s overall disease state (20). Below in figure 1 is a hand picture of a patient with RA and their wrist MRI showing synovitis with associated erosions and bone marrow oedema (BME).

*Figure 1: Patient with Rheumatoid Arthritis*
On the left, is a right hand picture of a study patient with Rheumatoid Arthritis with swollen wrist, 2\textsuperscript{nd}, 3\textsuperscript{rd} and 5\textsuperscript{th} metacarpal phalangeal, and 2\textsuperscript{nd} to 4\textsuperscript{th} proximal interphalangeal joints; and on the right, is the wrist MRI scan of the same patient showing erosions (white arrow), bone marrow oedema (arrow head) and synovitis (white star).

1.3 Disease Activity in clinical practice:

The initial clinical diagnosis of RA is based on combination of patient symptoms, examination and biochemical analysis. The diagnosis was previously assessed against the revised ACR criteria ‘87 (18) and now the 2010 ACR-EULAR criteria (19). The new 2010 criteria, as compared to 1987 criteria, classify more patients with RA and also those with earlier disease (43).

In RA, inflammatory activity cannot be assessed by one single measure (44). The currently accepted clinical assessment of a patient’s disease is based on clinical history, assessment of joint tenderness and swelling, the 28 joint disease activity score (DAS 28) (45), blood biochemical markers (ESR-erythrocyte sedimentation rate and CRP- C-reactive protein (46, 47)) and patients own assessment of their disease state.

ESR and CRP are descriptive biomarkers in RA as they describe the state of the disease and are not involved in the pathogenesis (48). Therefore, only limited information can be obtained from these. ESR and CRP reflect disease activity but have been shown as unreliable tools for predicting long term disease progression (49). Combinations of these are more reliable than any one parameter by itself (45, 50, 51).
1.3.1 DAS 28:

The Disease Activity Score (DAS) is a clinical index of RA disease activity (44). The 28 joint disease activity score is calculated based on a formula, which uses the number of swollen and tender joints (out of 28 joints), ESR, and a visual analogue score (mm). Scores range from 2-10. Low disease activity is scored ≤3.2, >3.2 and ≤ 5.1 is moderate disease and >5.2 is severe disease (45, 52).

1.3.2 Joint Damage:

Joint destruction can present a number of difficulties to clinicians, as joint destruction can continue despite low levels of disease activity; whilst in other subjects there is no joint destruction despite high levels of disease activity. A well-known feature of RA is the fluctuation of the disease activity with stages of flares and remissions.

1.3.2.1 Joint damage and function:

The natural history of RA is of progressive articular damage and gives a cumulative picture of disease activity (53). In the early disease phase articular damage can be of varying severity (54). Welsing et al, looked at the relationship between disease activity, joint destruction and functional capacity, as assessed by the Disease Activity Score (DAS 28), modified Sharp scoring (a radiograph scoring method) and a health assessment
questionnaire disability index (HAQ DI), over the course of RA. In early RA, functional capacity is most associated with disease activity, and in late disease state, with joint damage (55). It is therefore crucial to identify the early signs of joint damage before the disease advances to late stage. Boers et al described that local expression of early RA disease at baseline and at the 1-year follow-up stage is strongly related to a progression of damage in the individual joint (56). The loss of functional capacity over the course of the disease is progressive and is directly related to disease activity and joint destruction.

1.3.2.2 Challenges in clinically assessing joint damage:

Clinical disease activity assessments and correlation with joint destruction can be challenging. As measures of joint swelling, tenderness and function, as well as laboratory measures which reflect synovial inflammation, can improve in patients whilst articular damage can continue (50). Despite its destructive potential, the course of RA can be quite variable. Some patients experience only a mild form of oligoarticular symptoms of brief duration and minimal joint damage, while others will have progressive polyarthritis and marked joint deformity (1).

Scott et al described significant improvement in clinical and laboratory measures in 64 patients observed over 1 year who had evidence of continuing joint destruction (57). They followed 88 RA patients treated over 10 years with a large number showing radiological progression. (57). In a vast majority of patients (70-93%) joint damage on X-rays is seen at
an early stage, even within two years of disease onset (58). Though, more recently with modern treatment strategies it is now increasingly difficult to see structural damage (59).

Molenaar et al, assessed 187 patients with RA in clinical remission and followed them clinically and radiologically for 2 years. They concluded that clinically relevant progression of joint damage occurs in patients with RA in prolonged remission (60). It has been described that despite clinical remission, histological and imaging studies showed persistently active disease (61, 62). Voskuyl et al, have also advocated adding radiographic assessments to the criteria of clinical remission (63). Presence of subclinical inflammation as seen on advanced imaging has been suggested as a cause for continued radiographic progression in clinical remission (64).

Factors such as the presence of Rheumatoid Factor, HLA-DR4, older age, female sex, insidious onset have been shown to predict more severe radiological destruction (50, 65). There is now international acceptance of a panel of clinical (45), laboratory (66) and radiological measures (67) which better reflect the overall disease process and outcome (50).

1.3.2.3 Early treatment strategies and joint damage:

It is now well known that early aggressive combination treatment in RA inhibits structural damage and reduces clinical symptoms (51, 68-70). Heimans et al, tested a matrix model of treatment in early RA or undifferentiated arthritis (UA) and concluded that known risk
factors for damage progression lose their impact with early remission steered treatment and rapid radiological progression may be phenomenon of the past (71). The newer treatment strategies are thus aimed at inducing remission early (72).

Various treat to target strategies using advanced imaging biomarkers have also been used to prevent progression of erosive change and increase remission rates (73).

We need specific markers indicative of joint destruction. Improved predictive markers would have great utility in both examining the effects of therapeutic intervention in clinical practice and in assessing novel therapies in clinical trials. The need for markers which predict progression during low clinical disease and drugs that prevent damage that are independent of disease activity has been postulated (60).

Brown et al, have shown that subclinical joint inflammation detected by imaging techniques explains structural damage in RA patients in clinical remission and advocate the use of imaging for accurate evaluation of disease status and predicting outcomes (62). With the advent of advanced imaging there is a potential to look for earlier measures of joint damage from what is already known, thereby expediting early and aggressive treatment and limiting future joint damage and deformity.

1.3.3 Osteoporosis in RA:

Osteoporosis is a condition characterised by low bone mass, and decreased bone strength. In RA osteoporosis can manifest in two ways: generalized osteoporosis, which may be a
result of immobility, disease related inflammatory process and treatments such as steroids; and periarticular osteoporosis/osteopenia, which is likely due to local release of inflammatory agents (74).

Generalised osteoporosis measured by bone mineral density (BMD) loss is a known extra-articular complication of RA (75). The prevalence of osteoporosis in RA is twice as high as in general population (76). It has been described that patients with RA loose axial and periarticular bone mass in early phase, with 1 year of disease (75). Laan et al., in their study selected 147 patients with recent onset RA and found that BMD decreased when compared to normal reference group and concluded that this likely to be due to disease dependent mechanisms (77).

Periarticular osteopenia and bone erosions are mainly correlated with disease activity (76). It is known that in RA there is local and systemic bone loss caused by increased osteoclastic activity (78). This increased activity also results in bone remodelling, erosion and periarticular bone loss (79).

Studies have shown the extent of osteoporosis and change in BMD in RA (80-82). Haugeberg et al., showed that there is 2 fold increase in osteoporosis in female RA patients aged 20-70 years in their representative population (81). In another study, Haugeberg et al., assessed 94 male RA patients and found 2 fold statistically significant increased frequency of patients with reduced bone mass for spine and hip (83).
1.3.3.1 Osteoporosis and fracture risk:

Patients with increased BMD loss seen in RA are at risk of fractures (84-87). Any bone is at risk of fracture when there is osteoporosis, but those that commonly affected are vertebrae, hip/femur, elbow/forearm, humerus, and ankle (88). It has been shown in recent studies that treatment with monoclonal antibody, Denosumab, that target the cell mediators (RANKL – receptor activator of the nuclear factor kappa-B ligand) in bone formation and resorption is effective in suppressing bone resorption, increase BMD, and has the potential in preventing progression of erosions in RA (89). As part of the FREEDOM trial, this treatment showed reduction in fractures in women with osteoporosis (90). Other treatments used in treating osteoporosis in RA included bisphosphonates and anabolic parathyroid hormone analogues, with newer agents being tested (91). These are crucial as patients with RA who suffer from fractures have a poor functional outcome.

1.3.3.2 Osteoporosis and functional impairment:

Increased osteoclastic activity in RA not only contributes to systemic bone loss but also local structural abnormalities in the vicinity of inflamed joints, including periarticular osteopenia/osteoporosis, bony remodelling and erosions (79). Iwata et al., in their study found that periarticular BMD in the forearm is closely correlated with joint destruction and functional impairment in RA (78).
Dogu et al., looked at the role of hand BMD as a marker for hand function in established RA. They found significant positive correlations between hand BMD and pinch strength as well as hand grip strength (92).

Deodhar et al., looked at hand bone loss and functional disability in RA patients. Significant correlations were seen between percentage change in hand BMD to physical function, hand function and health assessment questionnaire at 5 years. The relative risk of bad hand functional outcome at 5 years was higher in patients with BMD loss higher than smallest detectable change, compared to patients with less BMD loss at initial 6 months (93).

1.3.3.3 Measuring bone mass:

There are various techniques that have been used to assess bone mass including X-ray (94-96), peripheral ultrasound (97), peripheral quantitative computed tomography (pQCT) (98), dual X-ray absorptiometry (DXA) (99-101) and digital X-ray radiogrammetry (DXR) (102, 103).

1.4 Imaging:

Efficient diagnosis and management of RA relies on sensitive imaging modalities to diagnose, monitor and prognosticate the disease in its various stages of disease course and activity. Early, aggressive therapy with disease-modifying drugs is important in optimising
the long-term radiological and functional outcome of patients with RA (104). In order to implement this strategy of initiating and adjusting early effective therapies in managing RA, we require sensitive imaging modalities using imaging biomarkers that can enable diagnosis and follow-up of the disease process.

The various modalities used as part of imaging RA joints are conventional radiographs (X-rays), Ultrasonography (US), Computerised Tomography (CT) and Magnetic Resonance Imaging (MRI). Historically changes on X-rays were considered gold standard in diagnosis and assessment of disease progression. Ultrasound has been shown to detect subclinical synovial inflammation using gray scale and power Doppler US (PDUS) (105) but is limited by lack of standardization, operator dependence, and inability to assess marrow changes. CT is considered the reference standard for erosion, but is limited by soft tissue and marrow analysis (106). While conventional X-rays only visualise the late signs of preceding disease activity, there is evidence for MRI being highly sensitive for early inflammatory and destructive changes in RA joints, and for MRI findings being sensitive to change and of predictive value for future progressive X-ray damage as explained in the sections below.

1.4.1 Conventional Radiography:

The conventional radiograph (X-ray) has been the traditional ‘gold standard’ imaging modality for assessing joint damage in RA (104, 107), both as a routine clinical diagnostic (18, 108) and prognostic measure (53, 109) and also as a measure in clinical trials (110-112).
1.4.1.1 Role of X-ray in RA diagnosis:

X-ray signs of RA include bone erosions, joint space narrowing (a sign of cartilage loss), and peri or juxta-articular osteoporosis (113). Historically, characteristic X-ray findings have been used in the diagnosis of RA as per American College of Rheumatology (ACR) modified criteria of 1987 (18). Small joints are most commonly affected in RA; this is also stressed by heavy weighting of involvement of small joints in RA studies (18, 107). Hence, for diagnostic purposes, symptomatic joints and joints typically involved in RA (feet and hand joints) are imaged (20, 107, 114). Brook and Corbett found that erosions first appeared in joints of the hand in 16%, of the feet in 36% and in both hands and feet in 48% of the patients in early RA (115). Another important advantage of imaging small joints is that the damage is much easier to detect than in larger joints (53).

1.4.1.2 X-ray in established RA

X-rays reflect the history of a joint pathology (104) and show evidence of cumulative damage to the joints (53), rather than the present ongoing disease activity. They depict the current status of a joint but do not reveal how and what imaging measures led to the joint damage.

Once established, the X-ray features of RA, namely erosions and joint space narrowing persist. It is known that persistent inflammation leads to (largely irreversible) joint damage.
As the disease progresses, the early radiographic features lead to joint instability, subluxation, and ankylosis (116, 117).

Van der Heijde et al., reviewed prospective studies over 3 year follow-up and found that 75% of the patients had radiographic damage, i.e. erosions, all of which could be identified within 2 years of disease (107, 118). During their entire follow-up, they found that foot joints erode earlier than hand joints (107, 118), and more foot joints were affected than hand joints (118). It has also been described that the extent of damage in joints of hands and wrists gives a good overall indication of both the extent of overall joint damage at a given time and the rate of progression of damage (53).

1.4.1.3 X-rays as a monitoring tool:

X-rays of hands and feet form part of pre-therapeutic documentation and assessments before commencement of disease modifying anti-rheumatic drugs (DMARDs). Radiographs also enable us to follow-up patients in clinics to assess DMARD efficacy in arresting erosion progression, influence dose change and select new DMARDs in the event of progression (109). Local therapeutic options in RA, like joint injection, synovectomy, or in advanced cases joint replacement, are also influenced by routine and follow-up X-rays of the joints.
1.4.1.4 X ray and joint function:

In RA, it is known that radiographic erosions seen early on in the disease duration are associated with long-term poor radiological and functional outcome (116). Healing phenomena of bone erosions in RA is rare (53). Radiographic bone erosions are only seen in a small percentage of early RA patients (119).

Fuchs et al., described that significant radiographic damage without mal-alignment could be seen within the first 2 years of early RA. They looked at quantitative radiographic scores for joint space narrowing erosions and mal-alignment in hands and wrists of 200 patients with RA. Most of the 42 patients with less than 2 years disease duration had radiographic damage, 28 had erosions, 35 with joint space narrowing, and only 1 mal-alignment (120). Plant et al., confirmed that a large proportion of joints become eroded in the first 2 years of RA (121).

Breedveld et al., described that greater joint damage at baseline was associated with poorer physical function at baseline with reduced improvement after treatment, underlining the importance of early intervention to slow down joint destruction. They used radiographic scores to evaluate joint damage (122).

Pincus and Callahan described that Health Assessment Questionnaire (HAQ) and radiographic scores of X-rays appear to be effective core set markers to document long-term progression of RA (123). Scott et al., described that joint damage and disability (HAQ
score) increase throughout RA duration and show strong correlation by 5-8 years. They concluded that joint damage is progressive, accounting for 25% of disability in established RA (124). Reducing joint damage in both early and late RA is crucial to maintain function (124).

1.4.1.5 X-ray semiquantitative analysis:

To assess X-rays over time, they need to be scored for comparison and to evaluate for disease progression. There have been various X-ray scoring methods used in the past like the Larsen score (125), the modified Larsen score (126), the Sharp score (127, 128), and the modified Sharp-van der Heijde score (117, 129, 130). The modified Sharp van der Heijde scoring uses hand and feet X-rays in chronological order and scores them for joint space narrowing (JSN) and erosions (131). This method is most appropriate for clinical trials where small radiographic differences are important (53).

Studies have also examined semi-automating assessments of joint space narrowing (132-136). A combination of scoring erosions and semi-automating JSN could also be an approach (132).

1.4.1.6 X-ray as an outcome measure in RA:

The role of X-rays in as a primary outcome in RA was assessed by Bruynesteyn et al and they investigated if radiographs showed joint damage with 3 months. They found that regardless
of baseline damage, in early RA 18% of patients had progression more than smallest detectable change; and in late RA 36% of patients had progressed (137). They proposed changes in RA can be detected within 3 months and this can be used in short term, randomised control trials with X-ray progression as an outcome (137).

As part of assessing outcome measures, it is important to assess smallest detectable difference (SDD) in radiographs which define significant progression (138). The SDD is also a useful measure in development of radiological response criteria (137, 138).

Radiographs have widely been used as an outcome measure in clinical trials using therapeutic intervention (139-144). The assessment of the effectiveness of therapy is important in trials of new molecules in the treatment of RA.

Hand and feet X-rays have been used a part of large clinical trials to evaluate other imaging modalities (110, 111, 116, 119, 145-147) and also as a measure in looking at radiographic progression with disease modifying agents and biologic therapies (148-150). It is clear that radiographs are a useful outcome measure which can be used to evaluate the natural history of RA, or to assess the effectiveness of therapy (53).

Studies have used X-ray features of joint damage i.e. erosions, JSN, subluxation or ankyloses as an outcome measure in radiographic progression. But it is known that periarticular osteopenia is one of the early features seen on radiographs and thus quantitative measurement of hand bone loss can be a useful outcome measure in RA (151).
1.4.1.7 Limitation of X-rays:

Though, the advantages of X-rays include their low cost, easy availability, reproducibility and existing validated scoring methods (53); their relative insensitivity to early bone damage, insufficiency in assessing soft tissue damage, synovitis and synovial hypertrophy, and limited views in 2 dimensional plane of 3 dimensional joints limits its use in early and sequential disease activity measure (109).

Early changes in RA are non-osseous in nature; Ultrasonography and MRI are superior to conventional radiography and CT in terms of detecting soft tissue inflammatory process. Ultrasound is user dependent, its use is limited to superficial joints, and more data is required from Doppler Ultrasound studies. MRI shows synovitis, bone marrow oedema, early erosions and tendonitis that are not seen on X-rays (152, 153). Also conventional X-rays requires an MRI estimated bone volume loss of 20 to 30% to allow certain detection, indicating MRI is a better method of detection and grading of erosions in RA Metacarpophalangeal (MCP) joints (111). MRI now has an established important role as an imaging biomarker in diagnosis and prognosis of RA.

1.4.2 Imaging hand bone loss in RA:

Periarticular bone loss affecting the small joints of the hands is one of the earliest features seen in RA (151, 154, 155), and is seen even earlier than generalised osteoporosis with
associations with subsequent joint damage and progression (156). Deodhar et al., have shown that patients with RA have significant lower hand BMD compared with healthy (157).

The various methods used to quantify peripheral bone loss in RA include X-rays, ultrasound, peripheral quantitative computed tomography (pQCT), dual X-ray absorptiometry (DXA) and digital X-ray radiogrammetry (DXR) with latter techniques being more commonly used (158).

1.4.2.1 Peripheral quantitative computed tomography (pQCT):

Peripheral quantitative computed tomography (pQCT), allows high resolution three dimensional measurement of bone microarchitecture and volumetric analysis of bone mineral density (159). When compared to DXA, pQCT is better at discriminating between women with and without fractures (160). pQCT, also offers potential in assessing components of bone strength with treatment. Burghardt et al., in a study using pQCT found that after 2 years of alendronate therapy (a bisphosphonate) there were significant improvement in BMD (161). The limitation with pQCT is that it only assesses bone at two sites of the peripheral skeleton – distal radius and tibia, and limited studies have shown this to correlate with axial skeleton (162). Another limitation is that it also uses ionising radiation, though at low doses. Further the images can be affected by various artefacts including beam hardening, scatter artefacts and other technical challenges including image analysis (159).
1.4.2.2 Dual X-ray absorptiometry (DXA):

Dual X-ray absorptiometry (DXA) or dual energy X-ray absorptiometry (DEXA) is the most common technique used to assess BMD. This method is used to assess axial (hips, and lumbar spine) or peripheral (forearm and hand) BMD. The technique uses low dose ionising radiation and is based on the differential absorption of X-rays as they pass through the bones so as to calculate T and Z scores. T-scores compares bone density with that of healthy young women and Z scores compares bone density with that of other people who are age, gender and race matched. A T score -1.0 or above is considered with normal range. A T score between -1 and -2.5 constitutes early bone loss and below -2.5 is osteoporosis (163).

1.4.2.2.1 Hand DXA and RA disease activity:

It is known that hand BMD loss is one of the early features in RA (93, 156, 164). Haugeberg et al., in their study looked at hand DXA in 74 patients with undifferentiated arthritis of less than 12 months disease duration. They concluded that hand DXA is a sensitive tool to measure bone loss in early RA. In a multivariate linear regression model they found C reactive protein (CRP) (p<0.001) and rheumatoid factor (p=0.04) to be associated with change in hand BMD in their longitudinal study (156). Hill et al., in their study showed baseline hand BMD correlated with baseline CRP (p=0.01) and 12 month radiographic score (p=0.02) (165).
In another study by Devlin et al., they showed that patients with higher CRP had significant lower hand BMD than those with normal CRP. Hand BMD correlated with disease activity, functional capacity and axial BMD (164). Lower periarticular BMD as measured by DXA, at metacarlo-phalangeal (MCP) and proximal interphalangeal (PIP) joints, has been seen in RA patients with higher total number of tender and swollen hand joints (166).

Tender and swollen joints are a clinical sign of joint inflammation in RA. Power Doppler ultrasound (PDUS) can be used to assess intra-articular vascularization and provides a semiquantitative measurement. The relationship of flow patterns and BMD using DXA was studied by Ozgocmen at al., (167) showing correlations with intra-articular bone and cartilage destruction.

As part of assessing outcome measures in RA therapeutic intervention, hand and feet radiographs are commonly scored using semiquantitative tools. DXA BMD measurement has been shown to as useful (168), if not more sensitive than radiographic damage scores (169).

**1.4.2.2 Hand DXA BMD and therapeutic intervention:**

Studies have evaluated DXA BMD loss in response to various therapeutic interventions (170-172). Haugeberg et al., explored the effect of intra-articular steroid on hand BMD. They found that intra-articular steroid over 3 months protects against periarticular bone loss in RA (171), thus highlighting the need to suppress inflammation in active disease to maintain bone health. Anti-TNF treatment has also shown to have effect on PIP joint BMD (170).
More recently, newer agents like Denosumab have shown to provide protection against erosion, and increase hand BMD (173).

1.4.2.3 Digital X-ray Radiogrammetry (DXR):

Digital X-ray Radiogrammetry (DXR) is a technique that provides estimation of BMD from geometric measurements automatically conducted from single hand radiograph. Historically, the radiogrammetry measurements were done using plain radiograph and simple measuring ruler (94). Rosholm el al., have previously described an automated digital X-ray radiogrammetric (DXR) method to assess bone mineral density loss for digital radiographs (103).

1.4.2.3.1 Comparing DXR and DXA:

DXR and DXA are different techniques of assessing BMD. DXR is based on geometric principles and measurements whereas DXA captures bone mineral density based on absorption of X-rays. Higher spatial resolution is obtained in digital radiographs used in DXR as compared to densitometry with DXA, which allows for better cortical and trabecular bone delineation and edge detection. DXR is also not affected by beam hardening and soft tissue thickness (103, 174). DXR can be performed on routine clinic radiographs whereas DXA requires patients to undergo the test specifically.
The DXR technique allows BMD measurements using computerised measurements looking at cortical bone thickness and porosity, which DXA lacks. It allows 2 routine X-rays acquired over time to be compared for BMD change and thus can allow wide degree of retrospective and prospective analysis and studies. The automated technique has also shown to have high precision (175).

Jensen et al., compared DXR and DXA to assess bone loss in unclassified polyarthritis and early RA. They studied 72 patients with symmetrically swollen and tender 2nd and 3rd MCP or PIP joints with 51 patients fulfilling the ACR criteria for RA and 21 patients with unclassified arthritis. They found that DXR BMD decreased significantly in RA patients and was associated with disease activity. Both erosive and non-erosive patients showed bone loss but this was greater in erosive patients. No changes were seen in BMD measured by DXA. They concluded that DXR was better than DXA for detecting and monitoring periarticular osteoporosis for the metacarpal bone (176).

In another study DXR and DXA were used to assess BMD loss of distal forearm (103). They found that BMD measurements using DXR correlated with DXA with steeper decline with age in BMD using DXR compared to DXA.

Hyldstrup at al., also found significant correlations between DXR and DXA, particularly at distal radius (p<0.0001). DXA was significantly dependent on body weight, height and surface area and DXR correlated with metacarpal bone length (177).
The advantage of DXR over DXA was also stressed by Reed et al., in their study of patients with fractures seen in clinic. They concluded that DXR may provide a feasible method for assessment of fracture risk and has the advantage of using standard clinical radiographs acquired in clinics (178). Dhainaut et al., in their study also found that DXR derived porosity is associated with distal radius fracture and might be a sensitive marker for skeletal fragility (179).

In patients with RA, Bottcher et al., showed that DXR based BMD can distinguish severity and progress of disease related periarticular osteopenia in contrast to DXA and concluded DXR to be a diagnostic tool in the course of RA (180).

1.4.2.3.2 Role of DXR in RA:

Periarticular osteoporosis is one of the earliest radiographic features in RA. DXR as a method of assessing BMD loss in RA has been extensively used (176, 180-187). The technique has also been investigated as a predictor of future erosions in RA (181, 188).

1.4.2.3.2.1 DXR and radiographic damage in RA:

DXR has been identified as a surrogate marker for radiological progression in RA (183). Radiographic scoring techniques can have limitations in evaluation of structural integrity as they provide semiquantitative scores. DXR measurements have been described to be more precise than radiographic scores (189).
Pfeil et al., assessed DXR as a surrogate marker for structural damage in RA and studied 94 RA patients. Metacarpal BMD was evaluated with DXR and radiographs were scored using Sharp scores. They found the Sharp scores showed no significant change over the study period of 22 months but there was minimal DXR BMD loss (183).

Stewart at al., in their study assessed 24 patients with early RA and found the computerised technique can predict at 1 year patients with become erosive at 4 years (181). Forslind et al., over 2 years, studied 166 RA patients from the BARFOT low does prednisolone trial. They found hand bone loss measured by DXR was seen in 64% of patients, and those patients have significantly more radiological progression than compared to patients without bone loss (p=0.012). Patients not treated with prednisolone had more bone loss than patients on treatment. They concluded that bone loss measured by DXR was an independent predictor of radiological damage and an important tool to guide treatment decisions (188).

Predictive value of DXR has also also evaluated by Hoff et al (190). They examined 1 year hand DXR BMD loss as a predictor of radiographic damage at 5 and 10 years. Patients with 1 year hand BMD loss were noted to have higher median radiographic scores at 5 and 10 years. In a linear regression adjusted model, DXR BMD 1 year loss was an independent predictor of radiographic outcome at 5 (p<0.01) and 10 years (p=0.02) (190). Güler-Yüksel et al., in their study investigated BMD loss and joint damage in first year of RA disease. 256 recent onset RA patients had baseline and 1 year hand BMD measured by DXR, with 68% patients showing accelerated BMD loss in first year. Hand BMD loss was associated with progressive joint damage at 1 year in hands and feet; and BMD loss in first year was a
predictor of joint damage at 4 years (191). Kapetanovic et al., in their study demonstrated early DXR BMD progression rate predicted joint damage at 1 year and upto 20 years in their early RA patients (mean duration 11 months) (192).

An association between hand DXR BMD and radiographic damage has also been shown in established RA patients with disease of > or = 5 years (182). DXR BMD has also been shown to correlate with X-ray semiquantitative scores in long standing RA (186).

Jensen et al., also showed in their study that DXR BMD and metacarpal cortical thickness were related to disease duration and erosions in RA patients. It was also noted that patients with erosive disease had lower values of BMD (184). Similarly, Bottcher et al., described that DXR can exactly quantify cortical thinning of metacarpal bones and bone loss in early RA patients surpassing DXA measurements at axial bones sites (185).

The role of bone loss as an outcome measure in RA was evaluated by Hoff et al, in their 2 year longitudinal observational study of 215 RA patients from the Oslo RA registry. DXR was used to measure cortical hand BMD and metacarpal index, and DXA was used to measure whole hand BMD. They found that bone loss could be shown over a 2 year follow-up when measured with DXR BMD (-0.9%, p<0.01), but not by DXA (0%, p=0.87%). DXA only showed bone loss in patients with < 3 years of disease duration, whereas DXR was independent of disease duration. They concluded that DXR BMD may be a more appropriate technique to identify RA related bone loss compared to DXA (187). Combining DXR with semi-automated analysis of joint space narrowing in RA has also been proposed as a diagnostic approach (193-195).
DXR BMD loss is also seen to be associated with disease activity (196), wherein increased disease activity and severity are associated with rapid bone loss. Dirven et al., evaluated if BMD gain occurs in RA patients in remission, given that inflammation results in increased bone loss. During 1 year observational period, they performed DXR BMD measurements on 145 RA patients with high, low disease activity and in clinical remission. They found 26% of patients in remission had BMD gain compared to 2% of high disease activity and 5% of low disease activity patients; and concluded that BMD loss is driven by inflammation (197).

The inflammation in bone is reflected as osteitis or as marrow oedema when imaged with MRI. Limited studies have assessed hand DXR BMD and MRI measures of disease activity (176, 198). Bøyesen et al., evaluated 84 patients with early RA (disease duration less than 1 year). Patients had baseline, 3, 6 and 12 months MRI, ultrasound, X-ray, and DXR BMD assessments. 67% patients had MRI erosive progression. A trend of higher MRI synovitis score and 3 month DXR BMD loss was seen in patients developing MRI erosions (198).

In RA disease activity, inflammatory cytokines are linked to increased bone loss (199). Bone inflammation or osteitis is seen on advanced imaging – MRI. Similar pathogenic mechanisms for hand bone loss and erosion in RA has been proposed (200). Further studies assessing DXR BMD loss and MRI features of osteitis would be helpful to understand the disease associations further both with and without therapeutic interventions.
1.4.2.3.2 DXR BMD and therapeutic intervention:

The ability to assess BMD on routine hand radiographs makes DXR BMD a potential tool in assessing RA therapeutic interventions. Güler-Yüksel et al., measured metacarpal DXR BMD and hip, spine DXA BMD change in 218 RA patients from the BeSt study at baseline, 1 and 2 years. They found that patients who had initial combination therapy with prednisolone or infliximab were associated with less hand DXR BMD loss compared to monotherapy (201). Hoff et al., in their study assessed effect of adalimumab on hand osteoporosis measured by DXR and concluded that this may be a sensitive tool for assessment of inflammatory bone involvement in RA (200). Prednisolone has been shown to decelerate RA disease related hand bone loss measured by DXR (202). Computerised DXR BMD measurements have also been used with newer therapeutic agent studies, like Denosumab, and shown growing evidence supporting clinical utility of DXR (203).

1.4.3 MRI:

1.4.3.1 Basic MR Physics:

The hydrogen atom is highly abundant in the human body and is the MR active nuclei used in most clinical MR imaging. MR active nuclei have a spin (measure of effective rotational motion), a charge and acquire a magnetic moment (i.e. they act like a small magnet).
MRI requires the subject to be placed in a strong magnetic field (strength usually measured in the standard international (SI) unit of Tesla). The stronger the field, the larger the net magnetization vector (NMV) produced by the hydrogen nuclei in tissue and the better the signal produced. MRI relies on the applied magnetic field being spatially uniform to obtain high quality images. In practice, the region of the MRI scanner in which the magnetic field is sufficiently homogeneous is at the centre of the magnet and is limited in extent – the very centre of this region of uniform field is called the isocentre. It can be a challenge in clinical imaging to get the whole region of the body being imaged close enough to the isocentre to achieve high quality results.

In equilibrium, the NMV points along the applied static field and is termed longitudinal magnetisation. A pulse of radio frequency (RF) magnetic field directed perpendicular to the main field can be used to rotate the NMV away from the main magnetic field. The angle through which it is tipped is called the flip angle (figure 2). The MR signal is due to the component of the NMV perpendicular to the longitudinal magnetisation (the transverse magnetisation vector) and it is detected by a receiver coil, which is usually specially designed to give optimal signal reception for a specific anatomical region of interest (in this study that is the wrist).
(a) Hydrogen atom has a spin and acquires a magnetic moment, (b) normally the atoms are orientated in different position and directions, (c) when placed in a magnetic field ($B_0$), majority of the hydrogen atoms align with magnetic field and this results in a net magnetisation vector (NMV), (d) The NMV is normally aligned longitudinally ($V$) with $B_0$, with application of a radiofrequency pulse this is flipped at an angle ($\theta$) and has a transverse component ($T$). The latter is detected by the receiver coil and a signal is produced.

Figure 2: Hydrogen atom and net magnetisation vector
After the RF pulse has been applied, the longitudinal magnetisation is reduced. T1 recovery is a process by which the longitudinal magnetisation recovers back towards its equilibrium magnitude. T2 decay is the decay of the transverse magnetisation (the signal) and is caused by interactions with neighbouring nuclei (figure 3). Different tissues have different T1 and T2 decay times and these also change when there is pathology present.

Figure 3: T1 recovery and T2 decay of different tissues following an RF pulse that creates pure transverse magnetisation with no remaining longitudinal magnetisation.

(a) The T1 recovery is a process by which the longitudinal magnetisation recovers back towards its equilibrium magnitude. (b) T2 decay is the decay of the signal over time. Differences in T1 and T2 times of different tissues and differences in these relaxation times between normal and pathological tissue are a primary cause of image contrast.

To produce a full image it is generally necessary to apply a repetitive series of RF pulses to manipulate the magnetisation, reading out some data during each repeat of the sequence.
Spatial encoding is achieved by the application of transient magnetic field gradients. Key parameters used to control the signals obtained from MRI scanners are the repetition time of the core sequence of pulses (TR), and the echo time (TE), which is the time delay between the excitation of the signal and when it is collected. The contrast produced between different tissues is dependent upon TR, TE, and the flip angle amongst other factors. This allows individual tissues and different structures across the body including bone, muscle, fat and fluid to be imaged.

To study the oedema inside bones that is often associated with RA it is useful to be able to suppress signals from fat. There are several ways to achieve this. Fat may be suppressed based on difference in resonance frequency with water and using frequency selective pulses or phase contrast techniques or inversion recovery sequences. Selective excitation of water is also a commonly used approach. Hybrid techniques combining several of these methods can also be used (204).

Two key measures of image quality are Signal to noise ratio (SNR), which is defined as the ratio of the amplitude of the signal received to the standard deviation of background noise, and contrast to noise ratio (CNR), which is a ratio between the difference in signal in two adjacent tissues and the standard deviation of noise.

When doing an MRI examination, it is necessary to decide what field of view (FOV) to use to achieve the required anatomical coverage and to set the image resolution voxel size – (a voxel is a volume element of an image). It takes longer to acquire images with smaller voxels and the SNR goes down as the voxels get smaller, so that selecting the
imaging parameters to use in an examination requires a trade-off between a number of factors.

MRI is often performed by acquiring signals one slice at a time to build up a stack of slices and so achieve a three dimensional (3D) coverage. It is possible to achieve 3D imaging directly by exciting a whole volume at a time and spatially mapping in 3D. The advantage of this approach is that the data can be viewed in any plane which is helpful for viewing and analysing complex structures like the bones and joints in the wrist.

1.4.3.2 MRI in RA:

MRI provides a promising alternative to X-rays for identifying and monitoring disease progression in RA (205-208). It is a proven very sensitive imaging modality for demonstrating anatomical joint change (205, 209-213), and has been shown to be more sensitive than X-rays for detecting joint destruction in early RA (49, 119, 147, 206, 208, 214, 215).

MRI provides tomographic images of a joint in various planes, excellent spatial resolution (216), better delineation and discrimination of various structures, including the joints, cartilage (215), tendons (217) and soft tissues (212, 218). Hand and wrist MR imaging has evolved immensely since early reports (205, 212, 219). Jorgensen et al., in their study of early RA patients (mean duration 4.8 months) found that 13 out of 15 patients had MRI abnormalities (212).
The abnormalities that MRI can detect include – erosions (205, 220-228), synovitis (205, 207, 208, 220-226, 229-237), bone marrow oedema (BME) (220, 222-224, 226, 238), and tenosynovitis (inflammation of the tendon sheath) (213, 226, 227, 239-244). MRI measures are reliable and correlate with clinical, laboratory and radiographic measures (245). The Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) group published a scoring system for MRI systems (RA MRI scores (RAMRIS)), which incorporates MRI features of erosions, oedema and synovitis (220).

It has been described that MRI is the method of choice for detecting early changes in RA, not only for its high sensitivity but also its ability to image after contrast enhancement and thereby providing more physiological characterization of the inflammation in the joints (246). Ranganath et al., in their review described that MRI was sensitive, and demonstrated erosions, BME and synovitis both in early and late RA, also in patients who have failed methotrexate or are inadequate responders to methotrexate or biologic therapy (226).

1.4.3.2.1 MRI Erosions:

MRI is a sensitive modality and is known to identify erosions much earlier than radiographs (205, 206, 221, 222, 228, 241, 247, 248). Radiographs lack sensitivity in early RA; MRI has the advantage of better soft tissue discrimination. Early studies have shown that MRI detected several carpal bone erosions on MRI compared to radiographs (205, 206).

McQueen et al., have reported that a high proportion of RA patients develop MRI erosions very early in the disease when conventional radiographs are frequently normal and that MRI
scans of the wrist at first presentation can predict radiographic erosions at 2 years (119, 146). Ostergaard et al., observed that MRI detection of new radiographic erosions preceded X-ray detection by a median of 2 years (247), thereby indicating the sensitivity of MRI. Poleksic et al., used MRI and X-rays to assess bony changes in knees in RA and found that in all cases, MRI was clearly superior (246).

Hoving et al., compared MRI, sonography and radiography for erosion detection (228). 46 RA patients with newly diagnosed RA (less than 2 years of disease) were followed up with radiographs, ultrasound and MRI at baseline and 6 months. Baseline erosions were seen in 85% of patients on MRI compared to 30% on ultrasound and 37% on radiographs. These increased to 91%, 41% and 48% for MRI, ultrasound and radiography at follow-up (228).

MRI also is known to identify erosions compared to radiographs in patients with disease remission. Chew et al., in their study found that 66.7% of patients in remission had erosions on MRI that were not visualised on plain radiographs (222).

MRI erosions identify areas of disease activity at the bone surface as opposed to directly imaging bone loss as in X-rays. MRI in addition to detecting more erosions than radiographs, also allows ability to differentiate erosions from cysts that can be commonly seen on radiographs (248). CT is known to be more reliable at detecting erosions and assessing bone structure (249, 250). Perry et al., in their study compared CT and MRI in assessing RA erosions (250). They found most erosions (87%) were identified by both CT and MRI, 9% on CT but not MRI, and 4% on MRI but not on CT. Overall erosion scores were higher on CT than MRI. Partial volume artefact and shift in slice position was the most common reason
for mismatch. Good interobserver reliability was seen for CT and MRI erosions (ICC 0.99 and 0.91 respectively) (250). Compared to CT, MRI has the advantage whereby it lacks the potentially damaging radiations used in X-rays and CT (107).

MRI erosions have also been used as a marker of disease activity while searching for new biochemical biomarkers. Fujikawa et al., looked at 98 patients with early RA, with disease duration less than 2 years, and assessed their DAS28, CRP, anti-CCP, matrix metalloproteinase-3 (MMP-3) and serum cartilage oligomeric matrix protein (COMP). They found that COMP values were statistically higher in patients with MRI erosions as compared to the one without erosions (251). Syversen et al. used longitudinal MRI at baseline, 3, 6, and 12 months to examine the extent of associations between serum or urine biomarkers with disease process in RA. They found baseline levels of biomarkers of cartilage degradation predicted structural damage progression, and serum levels of MMP-3 amongst others were longitudinally associated with joint inflammation (252).

1.4.3.2.1 Predictive value:

Baseline MRI erosions are known to predict future joint damage and also in development of RA in undifferentiated arthritis. A study by Li et al., looking at early predictability of RA in the absence of serological markers and absence of radiographic erosions in undifferentiated arthritis showed that patients diagnosed with RA on follow-up had significantly higher erosions in the wrists on MRI (253).
Studies have also described that baseline MRI erosions predict future erosion progression (254-256). MRI erosions predict radiographic erosions at 6, 12 and 24 months, respectively, (sensitivity 0.75, 0.6, 0.75), specificity (0.93, 0.94, 0.94), positive predictive value (0.086, 0.1, 0.17) and negative predictive value (0.99, 0.99, 0.99) (255). In another study by McQueen et al., it was seen that baseline erosion score predicted radiographic erosions at 2 years (p=0.04), with a sensitivity of 0.8, specificity 0.76, positive predictive value of 0.67 and negative predictive value of 0.86 (146).

**1.4.3.2.1.2 Treatment response:**

MRI is known to have a role in the assessment of RA disease, selection and assessments of patients with more or less aggressive treatment (146). Erosions can lead to joint damage and disability in the long term; but with new therapeutic agents erosion progression can be stalled, though healing process is rare (257, 258).

In a longitudinal study assessing anti-TNF treatment, MRI erosions showed low responsiveness to treatment at 3 and 6 month follow-up (259). Cohen et al., in their study used Denosumab at different dosages and assessed MRI erosion scores at 6 and 12 months. There was reduced rate of increase in erosion scores with higher dose of the drug (260).

Migliore et al., in their pilot study found no evidence of erosion healing over 12 months when patients were treated with anti-TNF or anti-TNF and Teriparatide (PTH1-34) (a recombinant form of parathyroid hormone). They found at 12 months the BME scores significantly improved and no new erosions were seen (261).
Lisboa et al., studied 29 biologic naive RA patients treated with anti-TNF and followed them for a year. They found that erosion scores did not change but other inflammatory scores decreased significantly (258). Only 1 patient (3.4%) showed erosion score decrease more than smallest detectable change.

Møller Døhn et al., showed regression of erosion scores in 1.6% of sites on CT, exceeding smallest detectable change, in RA patients treated with adalimumab (anti-TNF), though repair was rare (257).

1.4.3.2.2 MRI Synovitis:

MRI has the ability of assessing synovial inflammation (synovitis). An inflammed synovium is thickened and shows avid post contrast enhancement. Use of the Gadolinium intravenous contrast agent is helpful in looking at synovial tissue, which is the main site of inflammation and joint destruction in RA. MRI contrast agents work by shortening the relaxation times of tissues relative to the local concentration of the contrast agents. MRI obtained a few minutes after intravenous contrast injection demonstrate enhancement of the acute inflammation tissue clearly demarcated from the intra-articular fluid (262, 263). MRI also offers the ability to assessing multiple joints on the same imaging plane.

Intra-venous contrast agents enable assessment of increased levels of vascular perfusion within the area to be imaged (208, 215, 230) with early results described by Reiser et al
They assessed 24 joint of patients with RA, before and after administration of intravenous gadolinium contrast agent and found that synovial proliferation exhibited a rapid and marked increase in signal intensity compared to muscle and soft tissues (232). Synovitis assessed by contrast enhanced MRI has been shown to correlate with macroscopic synovitits on miniarthroscopy (264).

Dynamic contrast enhanced MRI (DCE-MRI) has been used as a quantitative measure in synovitis (229) and has been proposed that it may be better than Doppler ultrasound with potential to be become a gold standard in clinical trials (229).

1.4.3.2.2.1 Role of MRI synovitis in RA Diagnosis:

MRI evidence of joint inflammation has a role in RA diagnosis in combination with other clinical features (207, 221). Sensitivity of MRI to detect synovitis in very early (mean duration 4.8 months) RA was initially described by Jorgensen et al (212). Sugimoto et al., in their study observed that the incorporation of MR imaging criteria of active synovitis into the ACR diagnostic criteria improved the diagnosis of early RA. They showed a sensitivity of 100% and specificity of 73% in diagnosing RA (207). In another study Sugimoto et al., evaluated 50 patients with polyarthralgia and performed contrast enhanced MRI of the hands. Bilateral enhancement in wrists, and/or MCP and/or interphalangeal (IP) joints was used as MRI criteria for diagnosis, with clinical follow-up till diagnosis was made. A final diagnosis was made of RA in 26 patients with MRI yielding correct diagnosis in 25 patients.
They concluded that MRI as part of the diagnostic pathway for early RA contributes to more accurate diagnosis and allows early treatment decisions.

The utility of MRI diagnostic criteria of synovitis with erosion or BME has been shown to be more helpful than anti-CCP antibody in confirming diagnosis of RA (265). Ji et al., assessed the role of MRI in confirming suspected RA when anti-CCP antibody and radiographic erosions were absent. 31 treatment naïve early inflammatory arthritis patients were involved in the study, at end of follow-up 22 patients were diagnosed with RA. RA group has significantly higher frequency of MRI evidence of symmetric synovitis (253).

MRI has also been shown to be useful in diagnosing early RA and distinguishing from chronic inflammatory joint diseases (248). In cases of clinical doubt, MRI now forms part of the EULAR recommendation for RA diagnosis (223).

1.4.3.2.2.2 Predictive value of MRI synovitis:

Synovitis assessed by MRI is known to be a predictor of joint destruction (208, 223, 236, 266). In an early study, Yanagawa et al., investigated 49 patients with RA who underwent post contrast T1 weighted images and it was seen that MRI of the carpus detected soft tissues changes and inflammation earlier than anything seen on radiography and suggested MRI as a possible predictor of joint destruction ((208). Inflamed active pannus as seen on contrast enhanced MRI is known to lead to erosive change (236). A recent review by
Colebatch et al., have shown that MRI synovitis is considered a predictor of future joint damage (223).

A systematic review looked at predictive value of MRI in development of RA in undifferentiated arthritis (267). It was shown that combination of MRI synovitis and erosions increased probability of developing RA. Absence of MRI synovitis or a distinct pattern reduced the probability of developing RA (267).

Gandjbakhch et al., assessed predictive value of MRI detected inflammation for radiographic progression in patients with low disease activity. They included 254 patients in a multivariate analyses and found synovitis was the only independent predictive factor. ROC analysis found a cut off baseline synovitis score of 5 out of 21. They also concluded that high synovitis scores predict radiographic progression and MRI should be included in future remission criteria for RA (268).

Conaghan et al., looked at the relationship between synovitis and bone damage (269). They showed that in early RA, synovitis is the primary abnormality and has a close relationship with number of new erosions. The area under the curve for MRI synovitis was the only significant predictor of erosion progression (p<0.007) (269). High baseline score (p=0.003) and poor improvement over first 24 weeks (p=0.003) has been shown to be independent predictors of radiographic progression at 1 year (270). Baseline synovitis scores (p=0.57) has been related to change in erosion scores from baseline to 2 years (271). Baseline and 1 year cumulative MRI synovitis has also been shown to independently predict 3 year radiographic damage (266).
Synovitis at radiocarpal, radioulnar and intercarpal-carpometacarpal joints is also seen to influence cartilage damage in RA (272). These studies provide evidence that MRI synovitis has strong predictive value in RA joint damage in the short and long term.

1.4.3.2.2.3 Role of MRI in detecting subclinical synovitis:

MRI has been shown to be sensitive and accurately reflects joint inflammation when compared to clinical examination (225, 238, 245, 273). MRI also objectively defines the extent of synovial enhancement. Clinical assessments are based on pain, joint swelling and examination which can be limited by observer error. Goupille et al., evaluated 12 RA patients with clinical examinations, disease activity biochemical measures and MRI of hand and wrists. They found swollen joint count was 59 on clinical examination compared to 162 joints on MRI with synovitis (238).

Dissociation between clinical and MRI disease activity measures was also described by McQueen at al (110). They found that in early RA total MRI and erosion scores progressed at 1 year despite falls in clinical measures (ESR, CRP and joint count) (110). It is also known that clinically relevant progression of joint damage occurs in patients with RA in prolonged remission (60) and despite clinical remission, histological and imaging studies showed persistently active disease (61, 62, 274, 275).
Brown et al., in their study studied 102 RA patients on conventional treatment and judged to be in clinical remission. They found that despite being in clinical remission, 19% had radiographic progression over 12 months and MRI synovitis at baseline were associated with progressive radiographic damage (p=0.002) thus reinforcing the utility of advanced imaging in accurate evaluation of disease status and outcome (62).

Granjbakhch et al., looked at the MRI characteristics of RA patients in remission (64). They included 294 patients in clinical remission (DAS28 < 2.6) or low disease activity state (DAS28 ≥ 2.6 but < 3.2), with wrist and MCP MRI data for 287 and 241 patients. They found that majority of patients had MRI inflammation - 95% had synovitis and 35% BME in clinical remission group and 91% with synovitis and 36% with BME in low disease activity group. The semiquantitative scores for synovitis were moderate and low for BME. Thus showing MRI can assess subclinical inflammation in majority of RA patients in remission or low disease state (64).

MRI subclinical inflammation in disease remission and correlation with biochemical assessment with interleukin (IL)-18 was performed by Chew et al (222). 54% of the patients had undetectable or very low cytokine levels indicating both clinical and biochemical remission. They found 92.3% patients had MRI evidence of synovitis and 76.9% patients have BME despite being in clinical and biochemical remission (222).

A study comparing synovial histology with MRI in patients with clinical remission was performed by Anandarajah et al (61). They analysed 15 synovial specimens from 14 patients in clinical remission and found 4 had severe, 6 moderate, 3 mild and 2 minimal disease
activity on histology. MRI depicted synovitis and BME was seen on 86% of the images, thus showing imaging and histological correlations of inflammation in patients with clinical remission (61). The role of MRI in setting ‘joint remission’ goals in addition to ‘clinical remission’ criteria has also now been highlighted more recently (274).

1.4.3.2.2.4 Role as an outcome measure in therapeutic intervention:

Inflammation seen on imaging has been proposed to be possibly more predictive of therapeutic response than clinical features of disease activity alone, and thereby having an important role in treatment response (223). The ability of MRI to detect inflammation in multiple joints, in addition to identify other associated abnormalities including BME and erosions makes MRI a good outcome measure for therapeutic intervention. Studies have demonstrated that scoring or quantifying active inflammatory pannus may represent useful means of evaluating disease activity after treatment (22, 276, 277). It is known that in joints which show active pannus by contrast enhanced MRI, progression of bone destruction is expected (236).

Lee et al., in their study assessed the efficacy of MRI in defining state of remission with treatment. 10 patients with wrist RA were evaluated before and 14 months after treatment with methotrexate and hydroxychloroquine. 4 patients achieved remission and showed decrease in synovial inflammation and BME with no new erosion (275).
MRI post anti-Tumour Necrosis Factor (anti-TNF) therapy has shown a decreased gadolinium uptake in dynamic contrast enhanced MRI in the past (278) and also a reduction in inflammatory synovial tissue has been demonstrated by MRI in RA patients treated with intra articular injections of symptomatic joints.

MRI measures of inflammation including synovitis have been found to be the most responsive measures when evaluating anti-TNF treatment (259). Hirose et al., in their study showed that MRI wrist synovitis scores reduced from 6.1 to 2.2 from 0 to 16 weeks after anti-TNF treatment (279). A study by Roimicher et al., performed scintigraphy using radiolabelled technetium 99m anti-TNF and MRI on 8 RA patients and found that tracer detected inflammation highly correlated with inflammation on MRI in active RA patients (273). Interleukin-6 receptor antibody, tocilizumab, has also shown significant improvement in synovitis scores in other studies (280-282). These studies thus highlight the role of MRI in biologic treatment and newer therapies.

1.4.3.2.3 MRI Bone Marrow Oedema:

MRI offers a unique ability to evaluate inflammation within the bone marrow, which appears as bone marrow oedema (BME) and shows increased signal on T2 weighted MRI and better seen on fat suppressed images (283-285). Initial report of MRI wrist marrow abnormality was described by Koenig et al., (216). BME is seen in wide variety of conditions and has a significant role in inflammatory arthritis (285, 286). Studies have shown that BME detected on MRI closely correlated with post-surgical histological findings of inflammation.
Jimenez-Boj et al., performed MRI on patients due for joint replacement. They found that fat rich marrow was replaced by inflammatory tissue, increased water content and thereby was bright on T2 weighted and inversion recovery images (284).

In undifferentiated arthritis, BME seen on MRI has shown to have a positive likelihood ration of 4.5 in developing RA (267). BME along with clinical features and positive serology has shown to predict progression to RA in 82% of patients with undifferentiated arthritis, showing a sensitivity of 81% and specificity of 82% (288).

### 1.4.3.2.3.1 Predictive validity of MRI BME:

BME seen on MRI correlates with severity of inflammation, joint destruction, clinical signs; and is a predictor of rapid radiological progression (241, 266, 271, 283, 289, 290). BME is also seen very early on in the disease process and is thereby an early measure which is only seen on MRI. It is known that there is a 6 fold higher risk of developing erosion at the site of BME (283). BME is also known to be an independent predictor of RA in early undifferentiated arthritis (288).

A significant association between bone oedema at baseline and erosions at 1-year has been identified. Boyesen et al., examined association between modern imaging and joint damage as measured by MRI erosive change at 1 year. They found that MRI BME was an independent predictor of MRI erosion (198). High baseline BME score (p=0.02) and poor improvement over 24 weeks (p=0.001) are independent predictors of radiographic
progression at 1 year (270). McQueen et al., described progression of erosions despite clinical improvement in RA. They followed a cohort of 42 early RA patients and performed contrast enhanced dominant wrist MRI. They found that 74% of patients as compared to 45% at baseline had erosions on MRI and only 28.6% of patients had radiographic erosions at 1 year (110), with significant association seen between baseline BME and erosions at 1 year.

Haavardsholm et al., studied 84 early RA patients (< 1 year) and evaluated them at baseline, 3, 6 and 12 weeks with radiographs, and MRI. They found 48% had erosion progression on radiographs compared to 66% on MRI, and baseline MRI (score > 2 units) was an independent predictor of erosion progression (241), and suggested MRI has the potential to help clinicians in determining which patient needs early and aggressive treatment to avoid long term joint damage.

Predictive value of MRI to erosions on CT was also assessed in a study by Dohn et al (291). They found patients with progression on CT had higher baseline BME scores and baseline BME was a predictor of erosive progression (291).

BME has also been shown to predict long term erosions. Palosaari et al., in their multivariate logistic regression model have shown that BME predicts 2 year erosion progression (OR 4.2, 95% CI 1.3-13.8) (271). In the CIMESTRA study, 130 early RA patients were treated with methotrexate, intra-articular steroid and ciclosporin or placebo-ciclosporin. They found that MRI BME score was the strongest independent predictor for radiographic progression at 2 years (289).
Baseline and 1 year cumulative MRI BME has been shown to independently predict 3 year radiographic damage (266). Baseline BME also predicts erosions in the long term at 5 years (290) and 6 years (292).

Evaluation of cartilage is more feasible with field strength MRI and allows assessments in joint damage. McQueen et al., looked at predictive factors for cartilage damage over 3 years using high field strength (3 Tesla) MRI. Baseline radius BME predicted increased cartilage damage scores at radioscaphoid (p=0.0012) and radiolunate joints (p=0.0001) (272). These studies have thus highlighted the predictive role of MRI BME in joint damage.

1.4.3.2.3.2 MRI BME and treatment response:

MRI BME is a feature of inflammation within the bone and treatment strategies have shown improvement in this measure (279, 293). Hirose et al., studied 10 early RA active patients who underwent MRI at 0 and 16 weeks after anti-TNF treatment. They showed that BME scores reduced from 12.8 to 6.2, with improvement in DAS28 score from 5.54 to 2.7 (279).

A study evaluated baseline and 6 months BME scores after treatment with interleukin receptor blocker, tocilizumab (293). 41% of patients showed baseline BME with reduction or disappearance of BME seen at 6 months in 32% of patients and significant improvement in the scores (p=0.04) (293). Suzuki et al., also used tocilizumab in their anti-TNF refractory
patients and followed them with MRI for 1 year. They also found significant improvement in MRI scores at long term follow up (280).

Ostergaard et al., assessed MRI verified response to certolizumab pegol therapy in RA (294). MRI scans were performed at week 1, 2, 4, 8 and 16. They found significant reductions in BME scores at 16 weeks (-2.5, p=0.031) (294).

Significant improvement in BME scores were also noted by Migliore et al., in their study of anti-TNF and Teriparatide vs just anti-TNF treatment in active RA (261). Thus indicating role of MRI BME in treatment response strategies and assessing new therapies.

1.4.3.2.4 MRI tenosynovitis:

MRI offers the ability to assess the tendons around the hand and wrist on the same imaging study while evaluating the joints. Tenosynovitis is defined as inflammation of the synovial lining of the tendon sheath (243). When inflammed the tenosynovium around the tendons become thickened and fluid filled resulting in localised swelling. There is high prevalence of tenosynovitis of the hand in RA (213, 226, 227, 239-244).

Wakefield et al., investigated frequency of finger tenosynovitis in early untreated RA (244). They assessed 50 patients with ultrasound and MRI and found that 64% of the joints in 82% of the patients had MRI flexor tenosynovitis compared to 28.5% of joints in 48% of the patients with ultrasound. Extensor tenosynovitis was also seen in 40% of joints in 72% of
patients on MRI compared to 7% of joints in 18% of patients on ultrasound. Thus showing that MRI is more sensitive in evaluating for tenosynovitis (244).

Rowbotham et al., showed that 47.7% of RA patients in their study had tenosynovitis of hand interosseous tendons (242). Flexor tenosynovitis has been shown to be a predictor of early RA (sensitivity of 0.6 and specificity of 0.73) in unspecified arthritis (240). Combining MRI tenosynovitis with positive rheumatoid factor or anti-CCP are strong predictors of early RA (240). In another study, Navalho et al., showed that in early polyarthritis flexor tenosynovitis was a strong predictor of development of RA (OR 5.09, 95% CI 1.62-16.05) (295).

Baseline MRI tendionapthy has also been shown to be a predictor of tendon rupture after 6 years (296). In an extension of the same study they observed that extensive bone oedema and erosions in wrists in early RA predicts tendon dysfunction and hand function at 8 years, but not the requirement for surgery (297).

Tenosynovitis in RA has been described to be associated with RA progression (217). Navalho et al., showed that tenosynovitis of the extensor carpi ulnaris (Odds ratio (OR): 3.21), and flexor tendon of 2nd finger (OR: 14.61) in the very early RA (< 3 months duration) and 2nd finger flexor tenosynovitis (OR: 9.6) in the early RA (duration between 3 and 12 months) were associated with RA progression (217).

MRI tenosynovitis also has a role as an end point in assessment of treatment response. Lisbona et al., evaluated active RA patients treated with anti-TNF + disease modifying agents
or just disease modifying agents and found that MRI tenosynovitis significantly reduced in
the anti-TNF group (p=0.01) after 6 weeks of treatment. Combing MRI tenosynovitis and
synovitis scores an even significant reduction was noted (298). In a study by Haavardsholm
et al., total MRI inflammation score comprising of synovitis, tenosynovitis and BME were
seen to be highly responsive to anti-TNF treatment (259).

1.4.3.3 Which joints to evaluate with MRI in RA?:

MRI is time consuming and in most studies only wrists or wrist and MCP are imaged. It is
known that feet joint damage progresses at an earlier rate than wrists and hands (107, 118).
Ejbjerg et al., compared the detection of structural damage progression as seen on X-rays of
2 hands, wrists and forefeet with the MRI of both hands (wrists and 2-5 MCP) plus unilateral
metatarsophalangeal (MTP) joints and MRI of one hand (wrist and 2-5 MCP). They showed
that there was no significant difference between the two MRI techniques and that both MRI
techniques were significantly superior to X-rays (145). Calisir et al., analysed hand and feet
MRI in early RA and found MRI detected synovitis and BME with no significant difference
between MCP and metatarsophalangeal (MTP) joints (224).

It has been noted that MRI of the dominant wrist may identify erosions earlier than plain X-
rays and identify those who need early and aggressive therapy (119). Koh at al., compared
dominant and non-dominant hands for radiographic progression and found that radiological
damage was worse with higher progression in the dominant hand (299). Dominant hand
MRI has also been used in many MRI studies in RA (73, 110, 237, 259, 270, 279, 293).
1.4.3.4 MRI Scanner:

MRI scanners are available in several magnetic strengths and configuration. The field strength may be high field (≥ 1 Tesla (T)), mid field (0.5 T – 1 T) and low field (≤ 0.5 T) (300). Although MRI technology has been available for 30 years, routine clinical use in RA patients is limited (152), but has been widely used in clinical trials. Many studies in RA have been performed using low field (111, 145, 234, 256, 301), high field 1.0 T MRI and 1.5 T MRI (22, 145, 301, 302), and more recently with 3 T MRI (272, 295, 303-309).

The limitations of the low field MRI is the low SNR. The lower SNR limits the spatial resolution that can be obtained and hence the quality of MR images. Another drawback of low field MRI is longer image acquisition time (152) and also higher doses of contrast agent would be required for synovial enhancement (301). With higher field strength, MRI images with improved spatial resolution can be obtained without an increase in acquisition time (310). It is known that the low field MRI have low sensitivity for the detection of bone marrow oedema (145) and thus may have limited value in RA imaging and prognostication.

3T MRI has been available for clinical use (311) for nearly a decade. Higher magnetic fields produce an increased MR signal and higher SNR (311), thereby allowing for superior resolution with good signal. It also allows for faster acquisition (311). 3T MRI has been shown to allow more detailed information about anatomic structures (306, 312).
Lichy et al., found that high-resolution MR imaging of arthritic joints of the hand at 3T, provided detailed information about bone destruction, synovial swelling and perfusion (313). Aoki et al., in their study showed that 3T MRI visualised synovium, cartilage, bone and soft tissues more clearly than 1.5T MRI (306). In a study by Wieners et al., it was observed that the image quality at 3T was superior to 1.5T (314). It has been seen that the SNR produced at 3T is up to 16 times higher than 1.5T (315), allowing for detailed bone structure analysis at isotropic resolution in quick examination time (315). The CNR is also improved at 3T with longer T1 relaxation times than 1.5T (311). Imaging with high SNR and better resolution becomes critical in studies when the focus of interest is disease change in a complex compound joint such as the wrist (314, 315), which is commonly involved in rheumatoid arthritis (316, 317). This modality has an important role to play in furthering translational research in musculoskeletal diseases (318).

**1.4.3.5 Receiver coil used during scan:**

An MRI coil is a device which picks up the signals from the imaged area and these are specifically designed for the anatomy of interest to give optimal SNR. Studies have used various different coils during wrist MRI; surface coil (22, 293, 308), knee coil (319), and dedicated wrist coil (110, 119, 146, 272, 293, 302, 308).

A recent study examined the influence of different MRI strengths, coil types and image resolutions on semiquantitative MRI assessment of bone marrow oedema (BME) and image quality. Krabbe et al., evaluated short tau inversion recovery (STIR) images on 0.23, 0.6, 1.5
and 3T MRI using flex coils, extremity coils at 0.6 and 1.5T and higher resolution coils at 1.5T. A total of 41 patients and 12 healthy controls took part and 338 STIR images were obtained. They found that image quality was lowest at 0.23T, BME scores were higher with extremity coils and smallest detectable difference was better at higher field strength MRI (308).

Eshed et al., looked at influence of field strength, coil type and image resolution on assessment of synovitis by non-contrast MRI compared to gold standard contrast enhanced MRI. Fair-good reader agreement was found between different STIR protocols and post contrast MRI, with best agreement being at higher field strength and using extremity coil. They concluded that field strength and coil type influence synovitis assessment, and these criteria’s should be taken into consideration while performing MRI in clinical practice and research trials (320).

1.4.3.6 Conventional Subject Positioning:

To acquire good quality images, without motion artefacts, the patient should be in an as comfortable a position as possible (321). For wrist examinations, various studies have scanned patients in different positions. The positions used in closed bore MRI systems include: ‘superman/swimmer position’ (prone with hand above the head) (22) and hand by the side of the body while lying supine (146, 272, 302, 322, 323).
1.4.3.6.1 Challenges with current wrist positioning:

MRI of the small bones in the wrist poses a number of imaging challenges. Firstly it is difficult to place the wrist close to isocentre in the magnet and as a result wrist images are often spatially distorted. This is a particular problem for 3T MRI since the region of sufficiently homogeneous field tends to be smaller than the hitherto more widely used clinical field strength of 1.5T. Common approaches are to place the hand by the side of the subject (146, 272, 302, 322, 323), which provides a comfortable pose, but places the wrist at the very edge of an operation field of view of the scanner. This position can also be technically difficult for patients with large body habitus, due to limited close MRI system bore diameter (324).

To get the hand closer to isocentre another approach is to adopt the so-called ‘superman/swimmer’ position (22, 324), in which the hand is placed at isocentre. This provides a favourable geometry for imaging but can be stressful for the subject being examined, resulting in tiredness and painful joints (324). This can potentially result in examination failures caused by discomfort (325). The ‘superman/swimmer’ position is particularly difficult to sustain for older patients, patients with inflammatory joint disease (326) or those with shoulder complaints (321). For patients with RA it is difficult to remain in a strenuous position for a long time during examinations (327). In a review of upper extremity MRI studies, it was noted that motion artefacts and incomplete studies due to discomfort were seen in upto 25% of patients (325, 328).
MRI imaging is significantly affected by movement, more so with T2 weighted images (as the patient needs to lie still the longest). This is particularly a problem for serial research studies as subjects may be reluctant to undergo repeat examinations. The problem is exacerbated because wrist examinations benefit from high resolution imaging which tends to be slow leading to the subjects having to endure prolonged periods of stillness in a potentially stressful pose and motion artefacts. Some sequences used to assess synovial enhancement in a dynamic fashion require patients to lie still as serial images are acquired (329) and small changes can affect quantitative analysis. Thus scanning these patients in a more comfortable position will help to reduce some of these limitations with current wrist imaging positions.

1.4.3.7 MRI semiquantitative assessment:

Semiquantitative scoring method for MRI disease activity measures was initially described by Ostergaard et al (330). The Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) group published a scoring system for MRI systems (RA MRI scores (RAMRIS)), which incorporates MRI features of erosions, oedema and synovitis (116, 220, 331). The imaging sequences suggested were a T1 weighted image pre and post gadolinium contrast intravenous injection plus a T2 weighted fat saturated sequence or Short T1 Inversion Recovery (STIR) sequence (116). They defined-

**Synovitis:** ‘an area in the synovial compartment that shows above normal post-gadolinium enhancement of a thickness greater than the width of the normal synovium’ (220, 332).
**MRI Bone Erosion**: ‘a sharply marginated bone lesion, with correct juxta-articular localisation and typical signal characteristics, which is visible in 2 planes with a cortical break seen in at least one plane’ (220, 332).

**Bone Oedema (BME)**: ‘a lesion within the trabecular bone, with ill-defined margins and signal characteristics consistent with increased water content’ (220, 332).

Erosions are scored for each bone (wrists: carpal bones, metacarpal bases, distal radius and ulna; MCP joints: metacarpal head and phalangeal base). A score of 0-10 was given to each bone, 0: no erosion, 1: 1-10% of the bone eroded, 2: 11-20% of the bone eroded, etc. BME is scored 0-10 for each bone (as for erosions), based on the volume of bone affected. 0: no oedema, 1: 1-33% of the bone affected, 2: 34-66% and 3: 67-100%. Synovitis is assessed in 3 wrist regions (distal radioulnar, radiocarpal and intercarpal-carpometacarpal joints) and each MCP joints. The first carpometacarpal and MCP joints are not scored (220, 332). The score for each area range from 0 -3, 0 is normal and 1-3 (mild, moderate and severe). A reference atlas allows for training and standardisation (331-333).

The OMERACT RAMRIS is now a well-established semiquantitative method of evaluating RA MRI wrist images and has been widely used in clinical studies (226). It has been shown to have high intra and inter-reader reliability with high level of sensitivity for change. In a review study by Ranganath et al., they found that 8 out 9 randomised controlled trials that used MRI scoring had high inter and intrareader ICC, 0.68-0.98 and 0.73-0.98 respectively (226). Haavardsholm et al., looked at reliability and sensitivity to change of RAMRIS score in multireader and longitudinal setting (334). 4 trained independent readers scored 10 sets of baseline and 1 year follow-up MRI wrist images. Intrareader ICCs were high, baseline and
follow-up for synovitis 0.89 and 0.9, for erosion 0.91 and 0.9, and BME 0.9 and 0.98 respectively. The smallest detectable change was low suggesting ability to detect changes over time. Interreader ICCs were high too, baseline and follow-up for synovitis 0.69 and 0.78, for erosion 0.83 and 0.73, and for BME 0.79 and 0.95 respectively. Thus emphasizing the role of RAMRIS in monitoring joint disease activity measures on MRI (334). The RAMRIS scoring has been widely used in clinical trials (226) and its treatment response on various MRI measures were described earlier in sections 1.4.3.2.1.2, 1.4.3.2.2.4 and 1.4.3.2.3.2. RAMRIS scoring requires user training and can take 5 to 20 minutes to score (335).

Various modifications to RAMRIS have been described. A modified RAMRIS scoring was proposed to assess less hand joints (RAMRIS5) (336). RAMRIS5 showed strong correlations with RAMRIS (p<0.001) at baseline and follow-up (336). Sewerin et al., proposed a combined hand and foot RAMRIS score (HaF-score) (337). A simplified rheumatoid arthritis MRI score (SAMIS) was proposed by Cyteval et al., and has shown to correlate with RAMRIS and take lesser time (2 to 7 minutes) (335). Another modification was proposed to assess joint space narrowing (RAMRIS-JSN) (338). RAMRIS-JSN has been shown to have high intra-reader and inter-reader reliability.

A MRI wrist cartilage scoring system was developed by McQueen et al. (304) and showed excellent reliability. A modified RAMRIS version for reduced field of view (RAMRIS-RV) to assess erosions on extremity MRI has also been previously described (339). RAMRIS-RV was seen to have excellent inter-reader reliability (339). Haavardsholm et al., also proposed a tenosynovitis semiquantitative scoring method and showed it had high intrareader ICC (median ICC 0.84-0.88) and acceptable interreader ICCs (median ICC 0.73-0.74) (340).
1.4.3.8 Quantitative Analysis of MRI:

1.4.3.8.1 Erosion:

MRI produces a large amount of information about joint damage. One of the challenges therefore, is to find an effective way of harnessing the information to provide a measure that could be applied in clinical trials (220). Quantifying joint damage is a challenge and direct measurement of erosion size is an alternative approach to scoring (341). Paul Bird et al., in their study showed that quantitative manual outlining (segmentation) measurement of MRI erosion volumes in RA patients is feasible, with high intra-observer and inter-occasion reliabilities. They produced similar correlations as compared to scoring. Although, they examined cross-sectional data, the hypothesis that computerised erosion volume measurements maybe more responsive to change in longitudinal studies still needs testing (342). In the current state and with long manual outlining times, it is difficult to recommend this method in clinical studies. They also felt that as computerised image analysis methods become available, the time required for analysis should improve (342). Poh et al., looked at reliability and longitudinal validity of segmentation method (343). They found that reliability of volume measurements were superior to RAMRIS (ICC 0.97 vs 0.52). The method had good performance metrics, and excellent intra and interreader reliability (343).

Dohn at al., investigated intra and intermodality agreement between CT and MRI erosion volumes at the MCP joints. CT, MRI, and X-ray detected 77, 62 and 12 erosions respectively. Erosion volumes were calculated on CT and MRI using manual outlining on coronal images. Total erosion volume on CT and MRI correlated (p<0.01), with MRI volumes correlating with
RAMRIS scores. There were high intra and intermodality agreements (344). Another study also assessed CT manual erosion volume measurements and found they correlated with RAMRIS score (345). Manual outlining is a potential source of error if the edges of erosions are incorrectly identified (342). Recently, a study evaluated manual outlining method on 3T MRI (303) and assessed erosions and BME. They found high intra-observer reliability for erosion and BME (0.99 and 0.99). The interobserver reliability for erosions were high too and comparable to RAMRIS but moderate for BME (303). An alternate method of assessing erosion dimension using a single maximum measurement has also been used and shown to correlate with RAMRIS erosion score (346).

Semi-automated methods in assessing erosion volumes have been described using MRI (323, 347). An automated method has also been shown in rat model (348). These methods of erosion volume estimation are limited by their inability to distinguish between BME and erosion (348, 349).

1.4.3.8.2 Synovitis:

MRI allows ability to perform quantitative analysis of synovium. The commonly used method to assess synovitis is semi-quantitative scoring - OMERACT RAMRIS (220). These synovial scores have been validated and widely used but are limited to defined areas in the wrist (distal radioulnar, radiocarpal and intercarpal-carpometacarpal joints) and provide a scale (0-3) of activity. They also require trained readers and lack ability to detect volumetric quantification of perfusion measures and small changes in synovitis (329, 350, 351).
Inflammatory activity can be estimated by quantifying the increase in early synovial membrane signal intensity after gadolinium injection (104, 276). The total volume of the synovium can also be assessed and quantified (104, 277).

Various methods of quantifying synovial inflammation have been described including manual outlining (segmentation), and semi-automated methods. Ostergaard et al., described a method of manual outlining the inflammed synovium (352-354) and showed its reproducibility including intra-observer, inter-observer and inter-MRI variations (354). A major limitation of the manual techniques is its time consuming (3/4 – 2 hours per joint) and thus automated techniques are necessary for quantitative measures to be used in clinical trials or possibly in routine practice (277). A semi-automated method of using post contrast image subtraction and counting the pixels with enhancement and classifying based on degree of enhancement has also been described (355).

An automated method to determine synovial volume on MRI based on pre-set post contrast enhancement thresholds has been described and compared with manual outlining technique (277). This method took 5-20 minutes compared to the more time consuming manual method, with good synovial volumes correlations. The inter-MRI variations were higher than manual method particularly due to malalignment artefacts. Limitations of this method included defining threshold levels, and slight movement can affect threshold segmentation analysis (277). DCE-MRI has also been used to perform computerised analysis of synovial inflammation.
DCE-MRI offers the potential to quantify perfusion in inflammatory arthritis, and is perceived as a preferred imaging technique in evaluating disease, with regards to synovitis (211, 262, 349, 351, 356-361), and bone marrow oedema (BME) (362). DCE-MRI involves rapidly acquiring T1 weighted images repeatedly before, during and after gadolinium contrast injection (363). Studies have also shown that DCE-MRI has a predictive value in future disease progression with regards to erosions (351) and correlates well with synovitis and BME scores (363). Cimmino et al, described that dynamic MRI can be used to discriminate between active and inactive RA (358).

The utility of DCE-MRI is limited by lack of appropriate analysis methods (363). Region of Interest (ROI) based analysis has been the focus of DCE-MRI analysis (277, 358, 364, 365), manual techniques can take a long duration of time 45-90 minutes as compared to around 15 minutes using automated methods (277). They require either a user defined ROI over the whole synovium on a slice or small ROI in most enhancing part of synovium. It has been shown that the reproducibility of this method for rate of early enhancement (REE) is poor (350), with size, position of ROI (364) and motion artefacts having an impact on variation in results of quantitative analysis (363). Rate of early enhancement (REE) corresponds to the slope of signal intensity time curve and rate of enhancement (RE) indicates the steady state of enhancement (363).

Studies have used single slice with synovitis to select their ROI location on dynamic images (366). This method is prone to partial volume averaging and loss of complete disease and joint characterisation. Also patient motion can affect image analysis using this method. Zierhut et al., described that using 3D and whole wrist imaging would have advantages in
DCE-MRI analysis by; reducing volume averaging, allowing better patient repositioning in follow-up scans and helping in motion correction (366).

Recently a computer aided technique has been described by Kubassova et al (329, 367, 368) which corrects for motion correction and uses automated voxel-by-voxel analysis of signal intensity vs time curves (329). This technique, Dynamika (www.imageanalysis.org) has been assessed with manual method and shown to have good reproducibility and nearly eliminates observer influence (350). The software allows for measurement of Maximum Enhancement (ME), which is the increase (%) of normalised signal intensity curve over a baseline; Initial Rate of Enhancement (IRE), which is the increase in signal intensity per second (%/sec). The Maximum enhancement (ME) and Initial rate of enhancement (IRE) measures obtained using the computerised method also correlates with the rate of enhancement (RE) and REE (350). The semi-automated DCE-MRI analysis is also known to provide fast assessment of synovitis (350, 361, 363) with correlations with semiquantitative RAMRIS synovitis and BME scores (363). RAMRIS synovitis score was also seen to correlate with enhancing pixels on DCE-MRI (369). The use of a motion correction technique in this method reduces the blur effect and significantly increases the signal-to-noise ratio (363).

Axelsen et al., in their study evaluated this technique with synovial histology (361). They included 17 RA patient undergoing knee surgery; synovial inflammation was determined by biopsy and histology. IRE measure was seen to highly correlate with grade of histological inflammation (361). Vordenbäumen et al., in their study also showed that DCE-MRI perfusion measures of RA finger joints reflects histological synovial inflammation (370).
In another study, Axelsen et al., showed that the DCE-MRI computerised method is a reliable and responsive tool for assessing treatment in RA (371). They performed DCE-MRI in 12 active RA knee joints before, 1, 7, 30 and 180 days after intra-articular steroid injection and found that all DCE-MRI parameters decreased at Day 7. There was high intra and inter-reader ICC (0.96-1) (371).

It is known that synovial uptake occurs in subjects who don’t have inflammatory arthritis. Studies have described synovial enhancement in healthy subjects (372, 373) and assessed using RAMRIS scores. Ejbjerg et al., showed that low grade synovitis like changes occur in healthy subjects and found 8.9% of joints affected in their cohort (373). No known studies have looked at quantifying it longitudinally using the DCE-MRI computerised method. DCE-MRI with computer aided analysis has been described as a sensitive tool for assessment of inflammatory treatment response and thereby early disease biomarker research (374). Prior to using this method in longitudinal studies it is important to evaluate what is the inherent change in the DCE-MRI parameters (how stable are these computerised perfusion measures) over time in healthy subjects where no change is expected but some enhancement can be seen and in RA patients on routine clinical care. This validation would be useful to define cut off levels for treatment strategies.

1.5 Study design

There have been many studies that have used semi-quantitative visual scoring, RAMRIS, but limited studies so far that used computerised analysis tools for MRI measures longitudinally
over time while imaging at short and long time intervals longitudinally on a higher field strength (3 Tesla) MRI.

The work has been presented as two studies – preliminary and main studies. The preliminary work was about development of a patient positioning device for wrist imaging, to be used in the main study. The main study was a longitudinal observational study of RA patients on routine treatment using 3T wrist MRI, hand and feet radiographs and analysis using exploratory and new computerised methods.

1.5.1 Hypothesis:

The major hypotheses were that

1) While imaging patients’ hands and wrist, a bridge device allowing patients to position their hands over their abdomen in a supine position will allow comfortable and quality image capture.

2) Computerised manual and semi-automated exploratory methods will allow bone segmentation for image analysis.

3) Change in metacarpal bone mineral density using computerised digital X-ray radiogrammetry technique predicts subsequent structural damage to joints in inflammatory arthritis as assessed by radiography and MRI.

4) Software analysis methodologies for quantitative assessment of inflammatory burden detected on MRI will provide data that is
   a) Stable over time in subjects without known inflammatory joint disease.
   b) Allows detection of change in subjects with inflammatory arthritis.
1.5.2 Objectives:

- To help develop and test a novel positioning device for improved MRI examination of RA in the wrist and evaluate its use in an observational study.
- To assess and compare computerised bone segmentation tools including manual and semi-automated techniques.
- To investigate MRI and radiographic measures in healthy subjects where no change in joint appearance is expected to occur.
- To investigate over time the fluctuation in clinical, biochemical and imaging measures of disease activity in RA patients on routine clinical care.
- To investigate variability of DCE-MRI analysis in RA patients on routine clinical care.
- To investigate the relationship of early 3 month metacarpal bone mineral density loss using digital X-ray radiogrammetry with MRI measures of change at 1 year.

1.6 Prior work already done

Work related to the preliminary study had already begun prior to my start. This included selection and testing of imaging coils and design of a patient wrist positioning device – the ‘bridge’.
1.6.1 Imaging Coils:

1.6.1.1 Knee coil:

Knee coils have been used in the past for wrist imaging (319). The usage of the knee coil to image the wrist was quite uncomfortable.

1.6.1.2 Surface coil:

SENSE Flex Surface coil – Medium (14 cm x 17 cm) and large versions (20 cm x 20 cm) were used. These coils were light and flexible, so allowed more options for patient positioning and could be placed very close to the anatomy under investigation. This gave it an advantage over the Knee coil which was designed for a larger anatomical region. Positions tested were:

(a) Hand resting on the pelvis – This gave rise to motion artefact.
(b) Supine with hand by the side – This position was uncomfortable.
(c) Supine with hand above the head – Also resulted in discomfort.

The results from these initial tests indicated that a different way to position the patient might be valuable. This led to the aim to develop a rigid device that would enable wrist imaging close to the isocentre and in a position of comfort.

1.6.2 Patient wrist positioning device (‘the bridge’):

The initial concept behind the need for a patient wrist positioning device ‘the bridge’ was already ascertained. The advantage of the bridge was to image the wrist in a position of
comfort, with the wrist being close to the isocentre of the bore of the magnet, while producing images with good resolution. An early concept design had been developed before I started and it was my role to facilitate developing this idea into a working device and to test it under clinical imaging conditions.

1.6.2.1 Early prototypes:

The bridge was made from Perspex plastic sheets, which were moulded into the structure. There were multiple stages of development. The penultimate version was a semi-circular arc structure with side panels attached onto either side of the rear end of the bridge. The platform was removable and attached to the sidewalls with the help of 4 bolts and nuts, 2 on either side. The side bolts allowed for adjusting the height of the platform. The platform had 4 openings in the form of diagonally oriented slots at the corners of a square (see red arrows in figure 4). These were used to insert the Velcro bands to hold the coil and the wrist in place (Figure 4).

Advantages of the bridge: The Bridge helped to image the wrist in a position of comfort. The early prototype demonstrated that the idea was feasible and was likely to allow the wrist to be stably held closer to the isocentre than would be possible without resorting to the ‘superman/swimmer’ position in which the subject lies supine/prone with hand above the head.

There were however clear limitations. The initial demonstration placed the wrist and coils on top of a platform for support and the removable parts were held in place by Velcro
straps. Placing the coil on top of the platform moved the wrist upward taking it further away from the isocentre. The use of Velcro straps to hold the wrist onto the bridge platform was crude and not a reproducible or measurable method.

Figure 4: Penultimate version of the bridge

Semi-circular arc structure with side panels attached onto either side of the rear end of the bridge. A removable platform was attached to the sidewalls with the help of 4 bolts and nuts, which allowed for adjusting the height of the platform. The platform had 4 diagonally oriented openings (red arrow) for Velcro straps which held the coil and the wrist in place.
2 METHODOLOGY
2.1 Preliminary Study:

To achieve the signal-to-noise ratio required to support high resolution imaging it is necessary to use a dedicated local receiver coil and this both adds to the complexity of the examination and can compound the difficulties in achieving patient comfort. To address the key challenges in achieving high quality imaging in an acceptable manner an exploration was conducted prior to the start of the main study to explore both which coils to use and to develop a novel approach to achieving a comfortable pose that can place the wrist close enough to isocentre for high quality imaging and still allow subjects to hold their wrists very still. To this end a dedicated patient positioning device was developed in the form of a bridge that supports the patients wrist in a dedicated receiver coil placed anterior to the abdomen but lifted just above the body to avoid transferring breathing motion.

This work was intrinsically multidisciplinary, with very close working between physicists, engineers, radiographers and clinicians to develop the device; test it and evaluate the patient experience. In this process I acted as coordinator, recruiter of subjects, and evaluator of images and participated in refining the design based on what I was able to learn from the clinical examination of the volunteers and patients who helped in the testing.

This study was done under the methods development ethical approval held by the Imaging sciences department (optimization of a new 3T magnetic resonance imaging (MRI) scanner and comparison with a 1.5T scanner, (REC ref no: 2003/6517)). All subjects were recruited locally and gave written informed consent.
2.1.1 MRI:

MRI scans were carried out on the 3 Tesla MRI scanners (Philips Achieva 3T, Best, Netherlands), in the Robert Steiner MRI unit and Neonatal Intensive Care Unit at Hammersmith Hospital. Similar to most studies conducted, the area initially chosen to be imaged was one hand including the wrist and the MCP joints (314, 375, 376). This anatomical coverage led to an imaging FOV of 170 x 150 x 120 mm. The next important determinant was the MRI coil to be used to image the wrist as part of the main study. Choosing the right coil was of paramount importance for image quality/resolution, SNR produced and patient comfort, thereby ensuring patient satisfaction and good results. Various coils were assessed for the above, as different types of coil have been used in different studies for imaging wrists (22, 110, 319).

2.1.2 Imaging Coils:

2.1.2.1 Wrist coil:

A dedicated wrist coil designed for imaging at 3T the “SENSE 4 channel Wrist coil” (3.0 T High resolution wrist coil, Medical Devices Corporation, Waukesha, Wisconsin, USA) was acquired specifically for the study. The FOV for the coil was 120 mm x 98 mm x 82 mm.
2.1.3 Patient Positioning:

2.1.3.1 Wrist coil:

The wrist coil was tested in different positions—prone with hand above the head (figure 6) (22, 375) and supine with hand by the side (figure 7) (146, 302, 322). These were the standard positions used in routine practice and studies. The wrist coil was also later tested in the supine position on the developed wrist support device. Performance of the wrist coil and medium sized flex coils was evaluated. Position was prone head first into the scanner with hand extended above the head; with the same AP offset relative to the isocenter for both coils used.

The images produced from the dedicated wrist coil were far superior as compared to the surface flex coil that had previously been used to image the wrist + MCP (figure 5). The improved signal-to-noise ratio provided by the dedicated wrist coil comes in part from it having a smaller sensitive region, which results in signal dropout in the MCP region. This was extensively discussed by the study group including Anshul Rastogi (AR), Joseph V Hajnal (JVH), Peter C Taylor (PCT) and study sponsor (GSK). As it is known that RA affects both the wrists and MCP, it was concluded that high quality images with good spatial resolution will provide a significant benefit for quantitative analysis. To acquire good quality images with coverage of both wrist and MCP would require a 2 phase study, with repositioning between 2 separate examinations either in one prolonged session or in two visits. A similar approach had been adopted by McQueen et al., (119). Since this approach would be very onerous for patients who might be in significant discomfort from their disease, it was decided to image
just the wrist using dedicated wrist coil in the main study. This would allow the optimal image quality to be obtained and it was concluded that a more targeted examination with higher image quality would likely provide a more informative feasibility study.

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**Figure 5: Side by side comparison of surface and wrist coils**

*T1w FFE images after image registration. Image on the left is acquired in *flex M* surface coil and image on the right in dedicated wrist coil. Wrist coil has good resolution at the wrist but fails at MCP joints. Courtesy: Lada V Krasnosselskaia*
2.1.3.1.1 Prone with hand above the head position:

The subject lay prone on the scanner bed, with hand above the head. The shoulder was outstretched and elbow in an extended position (superman/swimmer). The hand was then placed on the lower half of the wrist coil with appropriate padding, it was checked that the ulnar styloid process was in line with the top pin of the coil connector. The top half of the coil was placed on top and side clips fastened. The coil was fixed onto the grooves on the bed platform for the coil. Patient position was as shown in Figure 6 below. The subject was then advanced into the scanner and images were obtained.

Figure 6: Standard position used to image wrist – prone with hand above the head
2.1.3.1.2 *Hand by the side:*

The subject lay supine on the scanner bed, with hand placed by the side of the body. The hand was placed in the coil as explained above and the coil was fixed onto the grooves on the bed platform. The shoulder was in complete adduction by the side of the body and elbow in complete extension. Patient position was as shown in Figure 7 below.

*Figure 7: Current alternative position used to image wrist – supine, hand by the side*

2.1.4 *Final version of patient wrist positioning device (‘the bridge’):*

2.1.4.1 *Development of the bridge:*

The initial concept behind the need for a patient wrist positioning device ‘the bridge’ was already ascertained and the penultimate design had already been developed (section 1.6.2).
This work was done in collaboration with physicists Lada V Krasnosselskaia (LVK) and Joseph V Hajnal (JVH) at imaging sciences department. Engineer David Woodman constructed the bridge positioning device. Perspex material was used to build the bridge. Several designs were developed by the team working together and tested for feasibility. The products used for the bridge development were plastics for larger components, nylon nuts and bolts, Velcro straps and adhesive material. All products used were MRI compatible. The development work involved exploring patient positioning and trial imaging experiments, with key factors being accommodating a range of subject size, minimising distance to isocentre and achieving flexibility in geometry to ensure sufficient articulation to accommodate relaxed poses for the wrist and upper arm joints. This was an iterative process that led to a final design which was then evaluated more systematically.

2.1.4.2 Evaluation of the ‘Bridge’:

The final version of the bridge was evaluated for comfort, image quality (Signal to noise ratio (SNR) and Contrast to noise ratio (CNR)) as compared to superman/swimmer and hand by the side positions.

Initially 10 healthy volunteers (7 males and 3 females; age range: 21-39 years, mean: 29.8 years) took part, but data was only available for 8 volunteers in all 3 positions (in the bridge, in superman/swimmer and hand by the side positions). 8 healthy volunteers* (6 males, 2 females; age range: 21-39 years, mean: 30.1 years, median : 30.5 years, *It was subsequently found that 1 volunteer had arthropathy), gave feedback data for the 3 positions by filling in a questionnaire that the author specially designed for the purpose. The
feedback evaluated the comfort level of 1-10, where 10 being the most comfortable, over the shoulder, neck, elbow, wrist and overall comfort.

SNR was extracted from these positions using the axial slices in 3 anatomical positions—radius, scaphoid and proximal 2\textsuperscript{nd} Metacarpal. CNR was also calculated. The bridge was also tested on 5 volunteers to check for reproducibility. Each subject was scanned on 3 different occasions. Using rigid registration, segmentation and transformation, the translation and rotations of 2\textsuperscript{nd} metacarpal, scaphoid and distal radius were calculated to check for reproducibility of pose. This analysis and measurements were done by the project physicist LVK.

In another trial for reproducibility of the bridge, individually moulded wrist support splints were used. These were abandoned after one trial in a subject as it was observed that rigid fixing of the wrist in the coil with the help of a plastic splint did not have a substantial effect in reducing the effect of movement at the elbow on the relative movement of the bones in the wrist.

\subsection{2.1.4.3 Image Registration:}

Image registration is a technique for aligning one image with another so that they can be compared in detail and consistent measurements can be obtained. An automated method proposed by Leung et al., used image registration and segmentation to assess change (348).
Rigid registration is a technique in which one image is matched to the other using only 3 translations (X, Y and Z axis) and 3 rotations (usually these are specified as one rotation about each of the three axes). The wrist changes pose between examinations, so a rigid registration of the whole image is not enough to correct for this. The approach used in this study was to segment each bone to be analysed so that they can be aligned individually. The registration technique was intensity based.

2.2 Main Study:

This was a single centre exploratory study and performed at the Kennedy Institute of Rheumatology Division, Charing Cross Hospital Campus, Imperial College, London, with imaging conducted at Imperial College’s Hammersmith Hospital Campus.

The study was approved by Riverside research ethics committee, reference 06/Q0401/97 (‘Clinical MRI in Rheumatoid Arthritis: An exploratory study to investigate disease activity in rheumatoid arthritis subject hand joints detected by magnetic resonance imaging (MRI) over a series of short time intervals and to correlate the findings to increased radiographic damage evident at 1 year’). All study patients gave written informed consent.

The study started in July 2007, after being delayed by issues with regards to the use of Gadolinium contrast agent and its safety which required substantial ethical amendments. The last study subject was imaged in July 2009.
The study design, hypothesis and objectives have been described in section 1.5, 1.5.1 (points 2-4) and 1.5.2 (points 2-6) respectively.

2.2.1 RA patients:

RA patients were referred either from their clinicians or self-referred by seeing study flyers. Due to the slow pace of referrals, various means were used for patient recruitment including patients highlighted in clinics by the author, recruitment talks to clinicians at various hospitals including Charing Cross, Hammersmith, St. Marys, Ealing, Chelsea and Westminster, West Middlesex, Watford General, Royal Surrey Hospital and West London Rheumatology Forum.

All patients upon referral were given a patient information sheet to go through. Once they decided that they wished to take part, they all gave written informed consent and were screened. This was done at Charing Cross Hospital. Subjects were recruited from July 2007 to June 2008.

2.2.1.1 Recruitment Target:

The sample size of 50 RA and 10 healthy subjects was based on cost and feasibility. The recruitment target was calculated by study sponsor (GSK). In the absence of directly applicable data, it was difficult to formally power the study. Simulation was carried out in order to assess what could be achieved with 60 subjects and to assess the conditions that
would be required to achieve at least 90% power to show that the overall correlation between MRI and radiographic assessments is greater than 0.5, using a two-sided test at a significance level of 0.10. Overall, this indicated that a study with 60 subjects should be able to detect the strength of relationship.

### 2.2.1.2 Inclusion Criteria for RA patients:

The inclusion criteria looked for RA patients who:

- Were ≥ 18 years
- Fulfilled the RA diagnosis as per ACR 1987 criteria
- Had a poor prognosis of structural damage as exemplified by – rheumatoid factor and/or anti-CCP factor positive, and/or at least two radiographic erosions
- Had recent active disease as evidenced by the Disease Activity Score (DAS 28) >3.2, C-reactive protein (CRP) ≥ 15 mg/l or Erythrocyte sedimentation rate (ESR) ≥ 28 mm/hr within the last 6 months
- Had a single swollen joint in imaged hand and would be able to complete the study.
2.2.1.3 Exclusion Criteria for RA patients:

RA patients were not eligible for inclusion in the study if any of the following applied:

- History of drug or alcohol abuse
- Contraindication to MRI or other MRI exclusions
- Allergy to iodinated and/or gadolinium contrast agents
- Creatinine clearance of <60 ml/min
- Steinbrocker function score stage IV
- Joint injection in the relevant hand in the 3 months prior to Day 1
- Pregnant or nursing females, and/or females intending on becoming pregnant during the course of the study
- Subject unable to position hand on the imaging splint
- Subject’s who were either receiving anti-TNF or other biological anti-rheumatic therapy or who had received such treatment in last 6 months prior to day 1 of the study
- Subject’s who had blood collection during the study that would lead to blood donation of over 500 mls in a 56 day period
- Any other subject the investigator deemed unsuitable for the study (e.g., due to either medical reason, laboratory abnormalities, not expected to complete 12 month time point or subject’s unwillingness to comply with all study-related procedures).
2.2.1.4 Study Visits for RA patients:

The subjects were to undergo a total of 6 visits including screening. At screening RA subjects underwent a process of consent, had a check on inclusion/exclusion criteria, gave medical history and underwent physical assessments. DAS 28 was calculated, routine bloods (Full Blood Count (FBC), Urea & Electrolytes (U&E), C-Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR), estimated glomerular filtration rate (eGFR)), Rheumatoid Factor, anti-Cyclic Citrullinated Peptide (anti-CCP) antibodies were checked. Hand to be imaged was identified based on most swollen MCP and wrist joints. For females a pregnancy test was performed. X-rays of hand and feet if required were obtained. Eligible subject underwent further study visits.

At Day 1, week 4, 12, 24 and 52 subjects had a MRI safety check done, medications were reviewed, DAS 28 was calculated, and physicians and patients assessment of the disease was performed. Routine and research bloods were collected, MRI wrist scan obtained, joint assessments (a 66 joint count on all visits except week 4, wherein a 28 joint count was done) & a Health Assessment Questionnaire (HAQ) completed. A Multi-assessment Fatigue (MAF) (377) questionnaire was completed at Day 1 and week 52. This was done as part of overall assessment of patient’s disease state. A pregnancy test was done for all females and any side effects were noted at all visits. X-ray of the hand and feet were taken at all-time points apart from week 4, this was done as it was uncertain how quickly our cohort would progress on radiographs. Digital photograph of the imaged hand was also obtained at screening and week 52. Table 1, shows detailed time point assessments.
<table>
<thead>
<tr>
<th></th>
<th>Screening *</th>
<th>Visit 1 * (Day 1)</th>
<th>Visit 2 * (week 4)</th>
<th>Visit 3 * (week 12)</th>
<th>Visit 4 * (week 24)</th>
<th>Visit 5 * (week 52)</th>
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<tr>
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<td>x</td>
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<tr>
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<td>Digital photograph of hand to MRI £</td>
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<tr>
<td>MRI of selected wrist £</td>
<td>x</td>
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<tr>
<td>Recording of side effects related to scan £</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>X-ray of hands and feet £</td>
<td>**</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<td>x</td>
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</table>

**Subjects who had not had hand and foot X-rays within the previous 8 months, at the discretion of the Investigator, had additional hand and foot X-rays at screening in order to determine whether they met the study inclusion criteria.  
* Each visit could be conducted over a period of more than one day in order to accommodate subject convenience.  
£ Assessments were done by study doctor (AR)  
$ Assessments done by study nurses  
® MRI scan was done with study radiographer (mainly Ms. Emer Hughes (EH))  
© Performed by radiographers at department of radiology, Charing Cross hospital, as per study protocol and technique

Table 1: RA patient assessments performed at each time point
2.2.1.5 Recruitment Challenges:

Recruitment was slow into the study in spite of extensive recruitment talks to referring clinicians. Interval ethics approval for various forms of recruitment adverts were obtained. The study inclusion criteria were also found to be rigid, which required patients to have both positive serology rheumatoid factor and/or anti-CCP in addition to radiographic erosions. This criterion was relaxed, and amended for erosions to only be necessary if serology was negative. The other challenges to recruitment included patients with claustrophobia, multiple study visits and thus patient time constraints. To accommodate the latter, reimbursement for patients’ time was also included.

In June 2008 the study sponsor decided not to continue to support the study based on the difficulty in subject recruitment to enable the objectives to be met and any further recruitment was stopped but allowed subjects in the study to continue. This resulted in a difficult situation with patients and healthy volunteers in the study undergoing visits. The academic interest in the study centred around exploratory and new image analysis techniques. After discussions it was decided that Imperial College would act as the study sponsor and see that these subjects complete all study visits. This required substantial ethics amendments and approval was obtained from the ethics committee.
2.2.2 Healthy Volunteers:

The study was approved by Riverside research ethics committee, reference 06/Q0401/97. Healthy subjects were recruited through flyers, personal contact and local advertisements. All subjects upon referral were given a patient information sheet to go through. Once they decided that they wished to take part, they all gave written informed consent.

2.2.2.1 Inclusion Criteria for healthy subjects:

The inclusion criteria looked for healthy subjects who:

- Were free from clinically significant illness or disease as determined by their medical history (including family), physical examination, previous laboratory studies, and other tests. Particular emphasis was put on the importance of excluding patients with any history of joint disease
- Were aged between 18-60 years
- Had a Body mass index (BMI) between 19-29.9 kg/m²
- Were capable of giving informed consent and comply with study requirements and timetable.

2.2.2.2 Exclusion Criteria for healthy subjects:

Healthy subjects were not eligible for inclusion in the study if any of the following applied:

- History of drug or alcohol abuse
- Contraindication to MRI and other MRI exclusion
- Known allergy to iodinated and/or gadolinium contrast agents
- Creatinine clearance < 60 ml/min
- Pregnant or nursing females, and/or female subjects intending on becoming pregnant during the course of the study
- Known history of arthritis or joint disease
- Subject unable to suitably position hand on the imaging splint
- Subjects who at day 1, have had a recent injury or swelling in the hand to be imaged

### 2.2.2.3 Study Visits for healthy subjects:

Healthy volunteers underwent 4 visits in total. At screening/Day 1 healthy subject’s gave written informed consent, study eligibility was assessed based on the inclusion/exclusion criteria, gave medical history and underwent physical assessments.

At all visits (Day 1, week 12, 24 and 52) healthy subjects underwent a MRI safety check, had a blood test to measure eGFR, underwent hand examination for pain or swelling, were checked for any side effects (related to the study participation), and had a MRI of the dominant wrist performed. Females had a pregnancy test done. X-rays of the hands and feet, and digital photographs of the imaged hand were performed on Day 1 and week 52. Table 2, details study visits for healthy subjects.
Table 2: Healthy subject assessments performed at each time point

**2.2.3 MRI Scan:**

Subjects, after having their eGFR results checked and MRI safety assessment done, were seen for the scan. They had a 22 gauge intra venous cannula inserted in the arm opposite to the one being imaged. A MRI scan was performed on the 3 Tesla MRI scanner (Philips Achieva 3T, Best, Netherlands) in the Robert Steiner MRI Unit at Hammersmith Hospital. A coil quality assurance test was performed by the radiographers each week before the scan. This was done by scanning a phantom in the wrist coil and checking its SNR. If the SNR...
changed by 25% then an element-by-element reconstruction was done to determine if there
was any evidence of a fault in any of the receiver channels.

The subject was placed feet first (i.e. feet towards the centre of the bore of the magnet) on
the bed of the scanner. They lay supine with the heels aligned to the edge of the bed. The
bridge was placed in the grooves on the bed and was able to slide over so as to straddle the
subject around the hips. A vacuum cushion bag was placed under the shoulder of the hand
to be imaged. It conformed to body shape and solidified when air was evacuated. The
subject was also asked to insert ear plugs and put on headphones through which music
could be played to reduce the sound made during the scan. The assembly of the bridge is
described in section 3.1.2.2.1.

The intravenous cannula was connected to the contrast injector (Medrad Spectris Solaris
MR Injection system). The subject was then advanced into the scanner.

2.2.3.1 Contrast Injection setup:

Study subjects were injected with the Gadolinium contrast agent (Magnevist, Bayer
Healthcare Pharmaceuticals, Germany) as part of the DCE-MRI scan acquisition using a
Medrad Spectris Solaris power injector. The amount of Gadolinium contrast (Magnevist 0.5
mmol/ml) injected as part of the scan was dependent on the weight of the subject. Prior to
every scan visit, it was ensured that the eGFR was more than 60 ml/min. The amount of
contrast injection was calculated as 0.2 ml/kg, with weight rounded to nearest 5kg. The
same amount of contrast was used at every visit, with the exception that if subject’s weight (rounded to nearest 5 kg) dropped more than 10kg then the amount was recalculated. The two syringes in the power injector were changed for every patient. The first syringe was filled with the calculated amount of the contrast solution. The normal saline flush was filled in the second syringe and worked as a follow through after the contrast. The injector was operated from the control unit placed outside the scanner room. The rate of contrast and saline infusion was 1ml/sec and the delay between the injection of the contrast and the start of the injection was 40 seconds. The contrast injection setup was performed by the radiographers. Figure 8 shows the complete set up before scanning a subject.

Figure 8: Subject positioning with wrist in ‘bridge’ device in the MRI scanner
Patient lay supine feet first on the scanner bed (green star); the bridge was placed in the grooves on the bed and was able to slide over so as to straddle the subject around the hips (orange arrow). The imaged wrist was placed in the dedicated wrist coil (green arrow), attached to a horizontal platform, which was placed into the side groove of the bridge. A vacuum cushion bag was placed below the shoulder of the hand to be imaged (blue arrow) for additional support. Tubing from contrast and saline syringes attached to Power injector (red arrow) was then connected to the intravenous cannula (black arrow). The patient bed was then moved to enter the bore of the magnet (yellow star) and imaging was performed.

2.2.3.2 Scanning:

Subject scanning was performed by the radiographers with the study doctor (author) present. After the subject details were entered, the exam card was uploaded. An exam card was an electronic folder containing all the study sequences with the same parameters used throughout the study. The sequences that were used were the ones that had been optimized prior to the study start. The sequences had been identified so as to allow RAMRIS scoring and optimised to improve resolution by changing scanning parameters and enable 3D imaging. The Philips proprietary name for 3D T1 weighted imaging used is FFE, which stands for Fast Field Echo. The T2 weighted imaging method used is called Turbo Spin Echo (TSE), which is a robust accelerated method that uses additional RF pulses to allow multiple lines of data to be read out in quick succession. As employed, this was not a 3D method, but rather individual slices that were acquired. The designed T2 sequence used an interleaved approach in which whole 3D volume was covered by overlapping slices, allowing data to be
viewed in multiple planes. During DCE sequence optimisation multiple parameters were adjusted to achieve the required balance between temporal and spatial resolution, coverage, signal-to-noise ratio, and image properties. To reduce the total time, TR was reduced, which decreased the SNR. To counter the reduction in SNR, TE was reduced, but with very short TE, water and fat were out of phase with one another, causing signal cancellation at water-fat interfaces and this proved an issue with image analysis. Hence, TE was raised to 2.1 ms so as to keep water and fat in phase and SNR was compromised. The acquisition matrix was selected to balance spatial and temporal resolution. Because 3D image resolution is important in the visualisation and assessment of complex bone conformations, modest reductions in voxel size in 3D had a large impact on imaging time. The imaging parameters were optimised by the project physicist (LVK). The sequences used in order are shown in table 3 and figure 9 below. The sequence parameters are shown in table 4.

<table>
<thead>
<tr>
<th>Scan Sequence</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survey Qbody</td>
<td>Preparation scan</td>
</tr>
<tr>
<td>Survey SWC (SENSE Wrist Coil)</td>
<td>Preparation scan</td>
</tr>
<tr>
<td>Reference</td>
<td>SENSE Reference Scan</td>
</tr>
<tr>
<td>1 T2wTSE SENSE</td>
<td>Multi-slice T2 pre-contrast</td>
</tr>
<tr>
<td>2 T1wFFE SENSE</td>
<td>T1 pre-contrast</td>
</tr>
<tr>
<td>3 DCE SENSE</td>
<td>Dynamic</td>
</tr>
<tr>
<td>4 T1wFFE SENSE</td>
<td>T1 post-contrast</td>
</tr>
<tr>
<td>5 T1wFFE_Proset SENSE</td>
<td>Proset Water select post-contrast</td>
</tr>
</tbody>
</table>

*Table 3: MRI Study sequences*
After the sequence 1 and 2 (T2w TSE and T1w FFE) the images were checked for their quality. If there was any movement artefact, then the sequences were rerun. The patient was then informed about the contrast scan. The control unit arm of the injector was armed and the DCE sequence and timer started simultaneously. After a delay of 40 seconds, contrast was injected while DCE images were continuously acquired every 10 seconds for the duration of the sequence. Following contrast injection, sequence 4 and 5 (T1w FFE post contrast and T1w FFE proset) images were obtained. The quality of the images was checked and subject brought out of the scanner. The images obtained were then anonymised by the radiographers and stored.

<table>
<thead>
<tr>
<th>MRI Sequence</th>
<th>Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2 weighted Turbo Spin Echo (T2w TSE)</td>
<td>TR: 9000 ms, TE: 55 ms, Flip angle: 90°, FOV: 120 x 97 x 82 mm³, Acquisition matrix: 208 x 168, number of slices: 140 (thickness: -0.58 mm, order: interleaved). The voxel size of the reconstructed matrix was 0.54 x 0.54 x 1.16, Time: 07 minutes 48.2 seconds.</td>
</tr>
<tr>
<td>T1 weighted Fast Field Echo (T1w FFE)</td>
<td>TR: 11 ms, TE: 2.3 ms, Flip angle: 20°, FOV: 120 x 98 x 82 mm³, Acquisition matrix: 240 x 196, number of slices: 164 (scan mode: 3D). The voxel size of the reconstructed matrix was 0.5 x 0.5 x 0.5, Time: 05 minutes 55.4 seconds.</td>
</tr>
<tr>
<td>(Pre and post contrast)</td>
<td></td>
</tr>
<tr>
<td>Dynamic Contrast Enhanced (DCE)</td>
<td>TR: 3.8 ms, TE: 2.1 ms, Flip Angle: 20°, FOV: 120 x 95 x 80 mm³, Acquisition matrix: 96 x 75, number of slices: 127 (scan mode: 3D). The voxel size of the reconstructed matrix was 1.25 x 1.25 x 0.63, Time: 06 minutes 52.8 seconds with 10 seconds temporal resolution</td>
</tr>
<tr>
<td>T1 weighted Fast Field Echo Proset (T1w FFE)</td>
<td>TR: 11 ms, TE: 3.5 ms, Flip angle: 20°, FOV: 120 x 95 x 80 mm³, Acquisition matrix: 96 x 75, number of slices: 127 (scan mode: 3D). The voxel size of the reconstructed matrix was 1.25 x 1.25 x 0.63, Time: 06 minutes 52.8 seconds with 10 seconds temporal resolution</td>
</tr>
</tbody>
</table>
Table 4: MRI study sequence parameters

<table>
<thead>
<tr>
<th>Sequence Type</th>
<th>Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2wTSE</td>
<td>98 x 82 mm³, Acquisition matrix: 240 x 196, number of slices: 164 (scan mode: 3D), Proset: water select, pulse type: 1331. The voxel size of the reconstructed matrix was 0.5 x 0.5 x 0.5, Time: 05 minutes 55.4 seconds</td>
</tr>
</tbody>
</table>

Figure 9: Study wrist image examples

(a) T2wTSE, (b) T1wFFE, (c) Dynamic Contrast Enhanced (DCE), (d) T1wFFE-post contrast, and (e) T1wFFE ProSet water select sequences
2.2.4 Scoring of Images:

2.2.4.1 OMERACT RAMRIS Scoring:

Anonymised, registered and aligned MRI images were scored using rview viewer (http://www.doc.ic.ac.uk/~dr/software/index.html). Scoring was done by two experienced (more than 5 years) radiologists (Keshthra Satchithananda (KS) and Adrian Lim (AL)). They underwent RAMRIS (332) training using the wrist imaging atlas (333) and read together a few scans for optimisation. After this the radiologists were blinded, and scored the MRI scans independently in a random fashion without knowing either the time point or disease status of the subjects. The MRI images were scored using OMERACT RAMRIS (332), which scores synovitis at 3 areas in the wrist, each scored 0-3, based on an imaging atlas (333). All 8 carpal bones, metacarpal bases and distal radius and ulna were scored for erosions. Scores were assigned from 0-10, based on the % of articular surface eroded, for example 0: 0%, 1: 1-10%, 2: 11-20%, .......10: 91-100% bone eroded or fused. Similarly all above bones were scored for BME (0-3), 0: no oedema, 1: 1-33% of bone involved with oedema, 2: 34-66% bone affected by oedema, 3: 67-100% bone affected by oedema. Maximum possible scores were Synovitis - 9, Erosions - 150 and BME - 45.

2.2.4.2 Van der Heijde modified Sharp Scoring:

All radiographs were scored in chronological fashion (131) using Van der Heijde modified Sharp (vdH Sharp) scoring, evaluating both hands and feet for erosion and joint space narrowing (53, 117). Scoring was conducted on the hospital picture archiving and
communication system (PACS) by two experienced (more than 5 years) radiologists (KS and AL), who underwent training for this scoring method. The radiographs were read jointly in consensus.

### 2.2.4.3 Computerised analysis methods:

Imaging data (MRI and radiographs) from the study were also assessed using computerised methods, and have been described in the subsequent results chapters.

- Manual and semi-automated bone segmentation technique – chapter 4. IxiView (IXICO Ltd, London) and SliceOmatic software 4.3 (TomoVision, Canada) were used for manual bone segmentation. Some of the initial image analysis and segmentation work, both manual and semi-automated techniques, were done in collaboration with IXICO Ltd., and physicists Kelvin Leung (KL) and Christopher Foley (CF). All segmentations were done by the author. KL did comparative segmentations while assessing interobserver variations of the methods. Rita Nunes (RN) helped with image registration while using SliceOmatic software to segment bones.

- Digital hand radiographs were analysed using automated software dxr-online – Chapter 5. The hand radiographs were analysed by SECTRA, Sweden, using dxr-online. This assessed metacarpal bone mineral density loss using digital X-ray radiogrammetry. This work developed academic-industry collaborations.

- Dynamic contrast enhanced MRI were analysed using Dynamika software – Chapter 6. Image Analysis, UK provided the software for analysis as part of collaboration. All the analysis was done by the author.
3 RESULTS 1: DEVELOPMENT OF PATIENT POSITIONING DEVICE
3.1 Preliminary Study:

Obtaining high quality images with positioning reproducibility at an acceptable level of patient comfort is of paramount importance in the field of clinical trials. This is particularly a challenge in the study of RA, as trial subjects are likely to suffer from chronic pain and may have limited mobility. Longitudinal imaging of the wrist for research and clinical trials using MRI requires the wrist to be placed in a comfortable position, close to the isocentre with high reproducibility. This chapter is based on the results from evaluating methods as outlined in the previous chapter.

3.1.1 Aims:

- To develop and test a support structure for MRI of the wrist to allow comfortable and reproducible examinations, thereby facilitating longitudinal studies.

3.1.2 Development of Patient positioning device ‘the bridge’:

3.1.2.1 Design criteria:

The following design criteria were developed during early phase discussions and were used to guide the development process:
1. Subject comfort during scan, to allow for longitudinal scanning and patient compliance.

2. To accommodate subjects of different body sizes.

3. To facilitate reproducible subject positioning based on measurable radiographic landmarks.

4. To ensure the hand/wrist is held firmly and still (without motion from e.g. respiration).

5. To work with a dedicated wrist coil.

6. To place the coil close to the isocenter of the magnet.

7. To allow precise control of the orientation of the receiver coil in the static field of the scanner to ensure the optimal coil performance (e.g. restricted to ±15°); and

8. Be easy to handle and operate

### 3.1.2.2 Final Version of the bridge:

The final version of the bridge was built keeping in mind the ability to obtain reproducible imaging, patient comfort and ability to image the hand close to the isocentre. At this stage the problem of supporting the dedicated wrist coil was tackled and also innovations were included to allow the coil and wrist positions to be recorded and reproduced from one examination to the next. A key change was replacement of the horizontal platform with a horizontal central crossbar. The semi-circular arc structure of the rear end of the bridge body was retained. The 2 side panels were similar in that they were attached onto the rear end. The shape was refined so that the sides cleared the scanner bore (hollow central part
of the scanner in which patients lies during scan). The side panel had slots into which the specially designed extended locking “wing” nuts of the central crossbar could be dropped (see white arrow in figure 10). The crossbar was attached to the upper half of the wrist coil from above. This allowed the wrist and coil suspended from the crossbar to move in the horizontal plane and, by adjusting the wing nuts, in the vertical plane. It also enabled the wrist to be suspended as close as possible to the anterior surface of subjects’ abdomen, and hence as close as possible to the isocentre. The revised design is shown in figure 10.

Figure 10: Final version of the bridge

3D model on the left and picture on the right; show the wrist coil attached to the central cross bar which was placed into the grooves of the side panel (white arrow) and with flexibility to adjust the lateral position of the coil and allowed rotation about horizontal (φ) and vertical axis (θ) axes
3.1.2.2.1 Assembly of the bridge during scan:

The wrist was placed onto the lower half of the wrist coil with the ulna styloid process in line with the upper pin of the coil (Figure 11). This was done for optimal imaging of the wrist and acted as an anatomical marker to prevent forward slip of hand during positioning. To prevent any flexion over the distal forearm a small sponge was placed between the edge of the coil and the palmar aspect of the wrist. Additional sponge could be placed over the dorsum of the imaged hand to make it secure in the coil. The whole crossbar with the attached upper half of the wrist coil was then placed on the lower half of the wrist coil with the wrist in it (Figure 12). The side clips of the coil were closed and the whole coil and crossbar with the wrist in place was then lifted, the supporting frame of the bridge was moved into position and the 2 side wing nuts of the crossbar were gently lowered into the groves in the side panels. This enabled the wrist to be positioned as low as possible for an individual subject, so as to place the wrist close to the isocentre during imaging.

To ensure reproducible positioning during repeat visits in longitudinal studies a measurement strategy was developed and a set of index markers designed and built into the bridge framework. On the occasion of each subjects’ first scan 7 measurements were taken. These measurements allowed wrist position to be reproducibly scanned during future visits. As the crossbar was attached on 2 wing nuts, they acted as hinges and allowed rotation about the horizontal axis. The wrist coil attached to the crossbar by a threaded stud which allowed rotation about a vertical axis (Figure 10).
Figure 11: Patient and Wrist positioning during bridge assembly

The bridge was positioned in the grooves of the scanner bed, with patient lying feet first. The wrist was placed onto the lower half of the wrist coil with the ulna styloid process in line with the upper pin of the coil.
During the evaluation phase of the bridge, work was done to look at how various measurements could help in ensuring imaging and radiography was reproducible over time. Figure 13 shows the measurements taken. The coil in the holder had ability to move in 2 planes (transverse/horizontal and sagittal/vertical), in the X and Z-axes. To allow these movements, measurements 1&2 and 3&4 were decided upon. Measurements (1) and (2) determined the lateral displacement of the coil mount from the left side of crossbar, at the distal and proximal end of the device. Measurements (3) and (4) determined the distance of the left side of crossbar from the top of the bridge at the distal and proximal end respectively. The height of the crossbar form the top of the bridge on the right side can vary during repeated exams and thereby change the distance of the wrist form the isocentre. Thus measurements of marked points on the left and right side of the crossbar were decided as measurements 5&6 respectively.
In addition the wrist is a complex joint with various degrees of freedom of movements, which cause change in relative positions of bones with respect to each other, so it was crucial to stabilise the wrist in the same position at every scan. Initially it was proposed to use wrist splints to try to prevent relative movement between the forearm and wrist. During a reproducibility study on 1 subject, it was seen that wrist splint did not make much of a difference and it was noticed that the wrist movement depended on the elbow joint position. Hence, elbow height from the MRI bed was decided as the 7th measurement to be used during patient positioning. Measurement (7) cannot be achieved by simply placing a ruler against the elbow because of the obstruction caused by the torso. To ensure this measurement was accurate, a specially designed device was created (as shown in right sided picture in figure 13).

Figure 13: Final wrist position in the bridge, with the 7 measurements for reproducibility
The first 2 measurements enable calculation of the angles of rotation in the horizontal plane. It is crucial to keep this angle ($\phi \leq 15^{\circ}$) (this is a specification imposed by the coil manufacturer). The measurement 3, 4 allow for calculating rotation in the vertical plane, $\theta$ which should also be less than $15^{\circ}$. A measurable difference between any of the above measurements (1 and 2 or 3 and 4) should be less than 2 cm to enable the angles being less than $15^{\circ}$.

To ensure patient comfort on repeat visits, the measurement values were reproduced and then the position of the whole bridge was adjusted in the head foot direction to allow the arm to feel relaxed while retaining the correct indexed positions. Straps and padding were added to support the upper arm so that the patient does not have to use any effort to retain the position.

3.1.2.2 Evaluation of the bridge:

3.1.2.2.1 Comfort and Image Quality:

Once the design of the bridge had been refined and tested informally as part of the development process, a more formal valuation was carried out. The position for scanning the wrist in the bridge (supine-feet first-hand in the bridge) (figure 8) was evaluated against the swimmers position (prone-head first-hand above the head) (figure 6) and hand by the side (supine-feet first- hand by side of the body) (figure 7). A set of anatomical images were obtained for subjects in each position. The order of positions were randomised between
subjects to remove fatigue effects. The imaging examination for each position took about 20 minutes.

8 healthy volunteers (6 male, 2 female; mean age: 30.1 years, range: 21 – 39 years). 1 subject was later found to have arthropathy. Subject comfort evaluation was done with the help of a questionnaire, for which the author got ethics committee approval. Subjects were asked to rate their level of comfort in the shoulder, neck, elbow, wrist and overall using a subjective self-assessed rating scale ranging from 1 (least comfortable) - 10 (most comfortable).

The comfort data (Table 5) showed that using the bridge was comfortable for the subjects over all the body regions- neck, shoulder, elbow, wrist and also overall comfort was better than the other two positions. The comfort at the shoulder was similar in both hand by the side and the bridge but the bridge was more comfortable in other joints and overall as compared to hand by the side. The hand by the side was comparable to the swimmers position for wrist comfort but was better for other joint and overall comfort. The bridge was also more comfortable than the swimmers position for all joint and overall comfort.
<table>
<thead>
<tr>
<th>Subject</th>
<th>Position (in scan order)</th>
<th>Shoulder</th>
<th>Elbow</th>
<th>Wrist</th>
<th>Neck</th>
<th>Overall</th>
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</thead>
<tbody>
<tr>
<td>1.</td>
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<td>7</td>
<td>7</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>swimmer</td>
<td>5</td>
<td>7</td>
<td>7</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td></td>
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<td>8</td>
<td>7</td>
<td>8</td>
<td>7</td>
</tr>
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<td>5</td>
<td>10</td>
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</tr>
<tr>
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<td>8</td>
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</tr>
<tr>
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<td>6</td>
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</tr>
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<td>6</td>
<td>7</td>
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<td>8</td>
<td>7</td>
<td>8</td>
</tr>
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<td>8</td>
</tr>
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<td>8</td>
<td>6.5</td>
<td>8</td>
<td>7</td>
</tr>
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<td>8</td>
<td>8</td>
<td>8.5</td>
</tr>
<tr>
<td>5.</td>
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<td>7</td>
<td>6</td>
<td>6</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>swimmer</td>
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<td>5</td>
<td>6</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
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<td>7</td>
<td>9</td>
<td>9</td>
<td>8</td>
</tr>
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<td>6</td>
<td>6</td>
<td>7</td>
<td>7</td>
</tr>
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<td>6</td>
<td>6</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td></td>
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<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
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<td>6</td>
<td>10</td>
<td>8</td>
<td>10</td>
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<td>6</td>
<td>10</td>
<td>8</td>
<td>10</td>
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</tr>
<tr>
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<td>10</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>8.</td>
<td>bridge</td>
<td>9</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>swimmer</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>by the side</td>
<td>8</td>
<td>7</td>
<td>5</td>
<td>8</td>
<td>6</td>
</tr>
</tbody>
</table>
Table 5: Bridge comfort results compared to other standard patient positions

8 healthy volunteers* along with comfort range, average for each joint and overall comfort for each position with standard deviation

The images acquired using the bridge had a higher SNR/CNR as compared to the hand by the side but lesser than swimmers position. This was because in the swimmers position the wrist was closer to the isocentre (table 6). The offsets with respect to the isocentre were extracted from the image data files. It was found that using the 7 measurements the reproducibility of the bridge was less than 1mm translation and less than 2° rotation, table 7. These analysis and measurements were done by the project physicist- LVK.

* One volunteer was later found have arthropathy.
<table>
<thead>
<tr>
<th>SNR (Signal to noise ratio)</th>
<th>Swimmer</th>
<th>By the side</th>
<th>Bridge</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.7±1.1</td>
<td>5.3±1.5</td>
<td>6.1±1.7</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CNR (contrast to noise ratio)</th>
<th>Swimmer</th>
<th>By the side</th>
<th>Bridge</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.0±0.5</td>
<td>2.6±0.5</td>
<td>3.1±0.5</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Offsets with respects to the isocentre (mm)</th>
<th>Swimmer</th>
<th>By the side</th>
<th>Bridge</th>
</tr>
</thead>
<tbody>
<tr>
<td>44.2±2.2</td>
<td>171.7±7.6</td>
<td>125.5±20.8</td>
<td></td>
</tr>
</tbody>
</table>

Mean ± std

Table 6: Bridge image quality assessments compared to other standard patient positions

<table>
<thead>
<tr>
<th>Bone Segments</th>
<th>Translations, mm</th>
<th>Rotations, degrees</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>X</td>
<td>Y</td>
</tr>
<tr>
<td>Radius</td>
<td>0.8</td>
<td>0.4</td>
</tr>
<tr>
<td>Scaphoid</td>
<td>0.6</td>
<td>0.2</td>
</tr>
<tr>
<td>2nd MCP</td>
<td>0.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Average over all bone segments</td>
<td><strong>0.5</strong></td>
<td><strong>0.4</strong></td>
</tr>
</tbody>
</table>

Table 7: Bridge reproducibility assessment

Averaged bone segment transformations for subjects scanned on 3 occasions shows less than 1mm of translation and 2° rotation.

Thus, this evaluation showed that though the bridge had lesser SNR/CNR as compared to the swimmer position, it was better on the comfort aspect. However the SNR and CNR were better using the bridge than with the hand by the side. It was decided that although use of the bridge would result in slightly less optimal imaging performance, there was likely to be a
net gain as a result of improved comfort, which was considered an important factor for any longitudinal scanning study, particularly as each examination was likely to last 45-60 minutes. The ability of the bridge to produce reproducible MR images was also likely to be a benefit that would facilitate comparisons between examinations of the same person and help in image analysis.

3.2 Main Study:

3.2.1 Comfort assessment of the positioning device:

The ‘bridge’ device was further assessed for comfort throughout the follow-up MRI main study which involved 5 MRI scans over the year for patients and 4 MRI scans for healthy subjects (Table 8). The results show that both RA and HV scored the bridge highly for comfort. The RA patients tended to rate comfort in the bridge device slightly higher than the normal controls, which provides some support for the decision to place a high weight on patient comfort in the evaluation of the bridge concept.
<table>
<thead>
<tr>
<th>Subjects</th>
<th>Visits (n=70)</th>
<th>Shoulder</th>
<th>Elbow</th>
<th>Wrist</th>
<th>Neck</th>
<th>Back</th>
<th>Knee</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA (n=12)</td>
<td>49</td>
<td>9.1</td>
<td>9.2</td>
<td>8.6</td>
<td>9.2</td>
<td>9.5</td>
<td>9.7</td>
<td>9.1</td>
</tr>
<tr>
<td>HV (n=7)</td>
<td>21</td>
<td>8.1</td>
<td>8.1</td>
<td>7.5</td>
<td>8.9</td>
<td>8.8</td>
<td>9.7</td>
<td>8.1</td>
</tr>
</tbody>
</table>

Mean results are shown. (0-10, with 10 being most comfortable). Mean age of subjects (patients: 53.8 yrs, healthy: 30.7 yrs).

*Table 8: Comfort score for the ‘bridge’ amongst MRI study subjects*

### 3.3 Discussion:

Obtaining high quality images with positioning reproducibility at an acceptable level of patient comfort is of paramount importance in the field of clinical trials based on a serial trial design. This is particularly a challenge in the study of RA, as trial subjects are likely to suffer from chronic pain and may have limited mobility (9). The wrist anatomy with multiple bones and articulations also possess a challenge as relative positions can change with small movements, thereby affecting computerised analysis.

MRI of the wrist has proved extremely uncomfortable for subjects who are usually asked to assume the “swimmer” or “superman” position (22), lying supine with hand above the head in order to place the region of interest close to the isocenter of the magnet (321, 324, 326, 378). This can usually only be tolerated for short periods of time, making it difficult to perform detailed examinations (325, 379).
Motion artefacts are known to degrade images in the ‘superman/swimmer’ position (380, 381). Berquist et al., in their review of elbow and wrist studies noted that motion artefact or incomplete studies were seen in 25% of cases due to patient discomfort (325, 328).

The ‘superman/swimmer’ position is uncomfortable and often patients can only hold still without moving the arm for a few image acquisitions at a time (321). In addition, the discomfort can potentially lead subjects to be reluctant to undergo follow-up examinations, undermining longitudinal studies. Studies sometimes use low field extremity scanners to solve this issue (378), such scanners have intrinsically lower signal to noise ratio and so force other compromises. There is also the challenge of vascular flow dynamic change with shoulder compression in the ‘swimmer’ position. We found in a healthy subject flow rate in brachial artery to be reduced by 25-33% by compression of superficial veins in the sitting and supine position. The swimmer position seemed to have a dominant effect on the flow rate in the brachial artery by superficial venous compression.

The ‘hand by the side’ technique (146, 302, 322, 323) requires patient to rotate the body so as to allow the hand to be as close as possible to the isocentre which is also a challenge in patients with joint pains. This is also not possible with increase body mass index (324). Patients are generally more comfortable in this position compared to the ‘superman/swimmer’ position, if they can fit in the scanner with the ‘hand by the side’ (379). One of the major drawbacks with this position is that as the hand is away from the isocentre, there is magnetic field inhomogeneity which can result in poor fat suppression (379).
To address these problems in a novel way and provide a solution that could facilitate use of higher field clinical MRI systems which offer the potential for higher resolution and improved contrast uptake sensitivity, we developed a ‘bridge’ device. During this project a prototype bridge was developed, evaluated and applied in an observational study. Subjects were able to maintain positioning for periods up to 45-60 minutes with favourable feedback on the comfort. MRI can be a challenge for subjects with claustrophobia (382), the supine feet first body position in the ‘bridge’ device can also potentially allow examination of even claustrophobic patients to some extent as the head is just at the edge of the scanner bore, though this hypothesis was not examined.

The magnetic field is most homogeneous at the magnet’s isocentre and worsens with distance away from it, although the local field inhomogeneity to a certain extent can be corrected by shimming. The bridge achieved a favourable compromise between the ‘superman/swimmer’ and ‘hand by the side’ positions. It improved on the swimmer position for comfort; allowed reproducible positioning, while achieving higher image quality than the hand-by-the-side approach.

The reproducibility and reduced motion artefacts help in quantitative image analysis where changes have a bearing in clinical follow-up and clinical trials. Imaging hand in a splint has been used to reduce motion artefacts and standardize position (322). Splint to fix the wrist in the coil was tried on 1 subject, and it was seen that wrist splint did not make much of a difference in fixing the position of the multiple bones in the wrist. Close inspection demonstrated that wrist position and in particular the relative locations and orientations of individual bones were easily modified by changes in position of the upper arm and elbow,
which constituted a very substantial lever. We found that rather than trying to hold the wrist in a rigid structure like a splint, it was both more comfortable and more reproducible to control the position of the elbow and through this the complete upper arm. Hence, fixing the elbow joint became crucial while using the bridge and elbow height from the MRI bed was identified as one the reproducibility measurement during patient positioning.

The ‘bridge’ device scored highly for comfort in the main longitudinal study, with patient’s and healthy subject’s average overall scores of 9.1/10 and 8.1/10 respectively. In addition to holding the wrist stably in a comfortable position as close as possible to isocentre, this study also addressed the challenge of ensuring reproducible positioning for longitudinal studies. A systematic set of measurements with associated tools was developed that allowed reproducible positioning to less than 1mm and 2°. Thus the developed bridge device offers a reproducible and comfortable alternative patient positioning method in wrist MR imaging.
4 RESULTS 2: ASSESSMENT OF SEGMENTATION TECHNIQUES
4.1 Introduction:

The main observational study was intended to identify structural changes associated with RA in the wrist, and perform analysis using exploratory and new computerised methods. An area of emphasis was to detect structural bone change from T1 weighted images.

To achieve these end points it was necessary to segment the images concerned to detect areas of change and to quantify the scale of change. The segmentations must be able to accurately delineate complex anatomical structures and distinguish one such structure from other similar structures nearby as well as working reliably on both normal and abnormal anatomy. Given the complexity of the task some initial evaluation work was done using manual and semi-automated methods as explained in the sections ahead. A key factor, given the number of images to be analysed, was the time taken to perform component tasks.

4.2 Aim:

- To assess and compare computerised bone segmentation tools including manual and semi-automated techniques.
4.3 Methodology development:

The method of segmenting bone maps/mask/outline and using image registration and transformation technique for future time points can potentially assess change in bone morphology, and disease activity including erosion. The following analysis methods were assessed for bone segmentation:

- Manual method involved drawing around the anatomy of each bone on each MRI slice. Two manual methods were tested:
  
a) Initial testing using Ixiview software (IXICO, UK) was performed on two healthy subjects. T1w pre contrast images were used.
  
b) Analysis using SliceOmatic (TomoVision, Canada). This method was used for segmenting masks of all bones on the baseline MRI of 8 RA subjects. T1w proton water select images were used. Using image registration and transformation technique visual comparison of disease activity change, over time was performed.

- Semi-automated method used region growing based on voxel intensity thresholding technique. We tested this method on 2 healthy and 2 RA study subjects for segmenting hamate bone and evaluated this method against manual technique. This analysis was done with team (KL, CF) at IXICO, UK.
4.3.1 Manual Segmentation:

4.3.1.1 Bone Segmentation on T1w pre contrast images:

Manual segmentation was used to extract bone masks from 2 healthy study subjects using T1w pre contrast images.

Segmentation was done in the following way:

T1w FFE pre contrast images were uploaded on to IxiView (IXICO Ltd, UK). The display magnification and contrast of the images was adjusted. Wrist images in the Coronal plane were used to segment the bones. Using the optical pen the margins of the bones were identified and traced around the bone directly on the computer screen. Segmented area and mask on a single slice is shown in figure 14. In a similar fashion the same bone was segmented in all the slices. The software had tools to propagate segmentations from a given slice to neighbouring slices, so providing a starting point to avoid restarting a fresh in each image. This was done for all 14 bones in the wrist, namely Scaphoid, Lunate, Triquetral, Pisiform, Trapezium, Trapezoid, Capitate, Hamate and the wrist articulating surfaces of radius, ulna, 2\textsuperscript{nd}, 3\textsuperscript{rd}, 4\textsuperscript{th} and 5\textsuperscript{th} MCP. The manually segmented areas were uploaded onto the IXICO, UK systems and volumes were generated automatically based on the bone masks and using the software. These volumes were generated by multiplying the volume of each voxel by the number of voxels.
4.3.1.1.1 **Advantages:**

- Allows bone delineation and volume measurements

4.3.1.1.2 **Disadvantages:**

- This method was time consuming and quite strenuous. The time taken to manually segment all 14 bones through all slices on a T1w pre contrast image of a single healthy wrist was quite substantial - 530 bone images took about 936 minutes (figure 15, and table 9). This was a major drawback and probably precludes there being a role for this approach in larger scale longitudinal studies or in the clinical setting. It can be noted that a disproportionate amount of time was taken to segment Trapezoid, Capitate and Hamate. The reason for this is the close proximity of other bones and difficulty to ascertain margins with the MCPs on the T1w FFE pre contrast sequence.
- User fatigue, shoulder and elbow strain while trying to precisely draw around the many bone images over long period of time (530 bones segmentations took 936 minutes).

*Figure 15: Manual wrist bone segmentation time graph*

*The total number of minutes taken to segment each wrist bone, against the number of slices per bone in a healthy subject (subject 2), using manual segmentation on T1w pre contrast images*
<table>
<thead>
<tr>
<th>Bones</th>
<th>Number of slices</th>
<th>Times in Minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulna</td>
<td>35</td>
<td>43</td>
</tr>
<tr>
<td>Radius</td>
<td>51</td>
<td>78</td>
</tr>
<tr>
<td>Scaphoid</td>
<td>49</td>
<td>62</td>
</tr>
<tr>
<td>Lunate</td>
<td>38</td>
<td>47</td>
</tr>
<tr>
<td>Triquetrum</td>
<td>32</td>
<td>55</td>
</tr>
<tr>
<td>Pisiform</td>
<td>30</td>
<td>28</td>
</tr>
<tr>
<td>Trapezium</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>Trapezoid</td>
<td>36</td>
<td>120</td>
</tr>
<tr>
<td>Capitate</td>
<td>38</td>
<td>105</td>
</tr>
<tr>
<td>Hamate</td>
<td>51</td>
<td>120</td>
</tr>
<tr>
<td>2nd MCP</td>
<td>37</td>
<td>68</td>
</tr>
<tr>
<td>3rd MCP</td>
<td>37</td>
<td>75</td>
</tr>
<tr>
<td>4th MCP</td>
<td>30</td>
<td>44</td>
</tr>
<tr>
<td>5th MCP</td>
<td>26</td>
<td>31</td>
</tr>
<tr>
<td>Total</td>
<td>530</td>
<td>936</td>
</tr>
</tbody>
</table>

Table 9: Number of slices segmented and total time in minutes per bone segmentation in healthy subject 2

4.3.1.2Manual bone segmentation using SliceOmatic software:

This method of bone segmentation created masks which along with image registration and transformation could allow comparison of bone morphology changes over time. It also could enable visual assessment of subtle changes in associated disease activity including erosion, BME and synovitis. T1w FFE Proset water select images were used due to their better bone edge delineation. SliceOmatic 4.3 Rev-6e software (TomoVision, Canada) was used for segmentation. After adjusting image, bone segmentation was done using the matrix generated by the software (Figure 16).
Figure 16: SliceOmatic bone segmentation masks

Image above with matrix that is used to aid segmentation and the image below shows final topographic image with segmented masks

8 RA study subjects had their baseline 8 carpal bones segmented in this fashion. The manually segmented maps were used to transform future time points (figure 17), algorithms for which were written by physicist in the department (RN). It was noted that better
alignment of future image was seen when it was transformed using the centre of the bone instead of the centre of the whole image, as given the multiple carpal articulations in the wrist each individual bone can move relative to the other.

Figure 17: SliceOmatic segmented bone mask and image processing
A. Segmented baseline capitate mask aligned on its baseline scan. B. Baseline capitate mask on a non-registered Week 52 scan, resulting is malalignment of the mask and bone. C. Baseline capitate mask on a registered week 52 image with globally transformed image, D. Same image transformed via capitate centre shows better alignment.
Using registered and transformed images visual comparison was made of images over time, evaluating for bone morphology, small changes in erosion size, associated pannus, and BME evolution. Examples for study subjects are shown in figure 18-20. It can be seen that small visual changes can be easily evaluated on this multiplanar analysis, with potential for volumetric analysis. This technique also has a potential role in assessment of early disease where it is crucial to follow change with treatment assessments.

4.3.1.2.1 Advantages:

- Visual comparative analysis
- Potential for bone volume quantification

4.3.1.2.2 Disadvantages:

- 2D segmentation
- Time consuming
- Required user to check scans
- Lack of complete automation
- Possible failure in advanced disease

Analysis done using this technique was also time consuming, figure 21 shows the slices/time taken bar chart for 8 study RA subjects. The total number of bone segmentation slices done was 2196 and time taken was 3256 minutes. We also saw that fused bones analysis posed challenges in analysis, and hence should be avoided in clinical trials as assessments for on-
going joint damage is difficult. This severely limits this method as a potential in regular clinical or large research studies.

Figure 18: Comparing Subject RA 2 over time

Image shows rigid registered Day 1 (A), week 4 (B) transformed via Triquetrum bone in subject RA 2. There is mild reduction in synovial enhancement at Triangular Fibrocartilage Complex at week 4 (red arrow). There is no difference in erosion size over this period.
Figure 19: Comparing subject RA 12 over time

Image shows rigid registered (b) week 4, (c) week 12, (d) week 24, (e) week 52 MRI to (a) Day 1, transformed via capitate bone in subject RA 12. Over the year there is changing pattern of BME in capitate. On Day 1 the BME has a predilection towards the distal end and over time there is some clearing from the articular margins at the distal end toward the proximal end. There is also reduced BME at proximal articular surfaces of 2-4th MCP. Between Day 1 and week 4 there is reduction in synovial uptake at distal triquetrum-hamate joint (red circle). This area has further uptake through the year. There is also reduced BME in triquetrum at week 4 which reappears at later time points. The RAMRIS scores mirror the registered images with Capitate scores day 1-week 24 (3-2.5-3-3) and Triquetrum (2.5-1.5-3-1.5-3)
Figure 20: Comparing subject RA 13 over time

Image shows rigid registered (B) week 52 to (A) Day 1, transformed via capitate bone in subject RA 13. Over the year there are some changes in capitate. As seen on the sagittal images there are new areas of BME on the palmar aspect around enlarging erosion (red arrow). Also there is resolution of the BME in the base of hamate at week 52 (white arrow). There is also less synovitis around 1st carpometacarpal joint (red circle)

Figure 21: SliceOmatic analysis - Total image slices segmented and time bar chart graph for study subjects

This shows that large amount of time was taken to segment all the carpal bones in each patient. The total number of bone segmentation slices done was 2196 and time taken was 3256 minutes. The largest amount of time was taken in subject RA5 who had fusion of all carpal bones.
4.3.2 Semi-automatic bone segmentation:

It was clear from previous work that manual technique was time consuming; semi-automated method potentially offers a quicker objective method of quantifying bone loss. In a small pilot study this method was compared to manual segmentation.

4.3.2.1 Methodology:

In this small pilot study, data from 2 patients and 2 healthy volunteers (n=4) enrolled in the main longitudinal RA MRI study was used. T1w FFE proset water select images (TE/TR/FA: 2.3 ms/11 ms/20°, 0.5 mm³ isotropic resolution) were used for the analysis. The hamate bone was segmented by two methods: manual and semi-automatic. The former method was performed using IxiView (IXICO Ltd, UK) as described in section 4.3.1.1. The latter used region growing based on voxel intensity thresholding technique (s/w from: http://www.doc.ic.ac.uk/~dr/software/index.html). The performance of two independent observers (AR and KL) was compared using difference in bone volumes (VD) (%) (mean±SD) and similarity index (SI) (mean±SD) (2x intersection / union of regions).

4.3.2.2 Semi-automated vs manual segmentation:

The total time taken for manually segmenting hamate bones (n=4) were similar between observers (AR and KL) (165 vs 132 minutes); corresponding times for semi-automated method were 10 and 8 minutes. Comparison of segmentations using similarity index and
percent volume difference (mean ± stdev) for two the observers for manual and manual vs semi-automatic method is shown in table 10. In the latter both volume difference sets have single outliers of near 19%, which greatly impacted the variability. Segmentations both manual and semi-automatic segmentations are shown in figure 22, the bone masks extracted using both techniques are similar when overlapped.

<table>
<thead>
<tr>
<th>Comparison type</th>
<th>Segmentation Method</th>
<th>Similarity Index (mean ± stdev)</th>
<th>Volume difference (%) (mean ± stdev)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inter-rater Manual</td>
<td>0.95 ± 0.01</td>
<td>8.07 ± 1.71</td>
<td></td>
</tr>
<tr>
<td>Intra-rater AR Manual</td>
<td>0.97 ± 0.01</td>
<td>2.08 ± 1.97</td>
<td></td>
</tr>
<tr>
<td>Between methods AR</td>
<td>0.93 ± 0.02</td>
<td>8.1 ± 7.9</td>
<td></td>
</tr>
<tr>
<td>Between methods KL</td>
<td>0.93 ± 0.02</td>
<td>10.6 ± 5.7</td>
<td></td>
</tr>
</tbody>
</table>

Table 10: Comparison of manual and semi-automated segmentation techniques
Figure 22: Comparing segmented masks using manual and semi-automated techniques

A: shows manually segmented hamate in a healthy subject. B: shows the same bone segmented using semi-automated tools and C: shows the two overlaid segmented volumes, manual (grey shading) and semi-automatic (white outline)

The semi-automatic method failed to extract bone volume in a subject with severe erosive disease. This is likely due to the failure of thresholding to work in areas of increased bone marrow oedema and severe erosive disease. Figure 23 shows an example of a T1wFFE water select image of a patient who has extensive erosions affecting the carpus, distal radius and 4-5\textsuperscript{th} Metacarpal bases. There is associated BME in the carpal bones and distal radius with severe synovitis. In such subjects the manual technique allows a way forward to extract bone volumes as shown in figure 24.
Figure 23: T1w water select volume sequence of a RA patient with advanced disease

The images show multiple erosions in the carpal bones, distal radius and 4-5\textsuperscript{th} metacarpal bases with marrow oedema and extensive synovitis.
Both the semi-automatic and manual methods performed well in normal subjects and patients with low disease, but the semi-automated method was much quicker. However in a case with severe disease, the semi-automated method was prone to error in regions of severe bone damage. This suggests that in large group of patients semi-automated would work well and occasionally manual methods may be needed in advanced disease, to ensure accuracy in all cases.
4.4 Discussion:

True volumetric analysis of bone morphology change due to erosions is a challenge even with the availability of high contrast and 3D imaging. Hodgson et al., described that there is little evidence of any improvement in accuracy by using volume measurements of erosions compared with OMERACT scoring. However, automated methods can provide potential time-saving advantages and do offer the potential to objectively measure bone volume loss in the future (349).

In this work it was seen that manual bone segmentation though can precisely delineate the bone, is time consuming which can limit its role in clinical and longitudinal studies. Long manual segmentation times have previously been described (322, 342). Good inter-reader and inter-occasions correlations were described as were correlations with erosion scoring (342). This technique is cumbersome, takes 5 times longer as compared to semiquantitative scoring (342) and causes user fatigue in analysis.

Coronal T1w images have been used to manually segment erosions in a study (322); in the authors experience using T1w images made delineation of bone margins difficult in distal carpal row and carpo-metacarpal joints. The use of T1w water select sequence made bone margin identification much easier.

Good inter and intra-observer correlation was seen for the manual segmentation method using the water select T1w sequence as this better defined the bone edge from synovial
tissue. Similarities were also seen in bone volume measurements between observers. Crowley et al., recently described manual outlining of erosion and BME for calculating volume, they found good inter-observer reliability for erosions and moderate for BME, reflecting difficulty to delineate borders of BME lesions (303). Bird et al., felt that despite good correlations this technique may not be feasible for multicentre studies due to issues with training and calibration (342), however an answer to this may lie in automating this process and centralising analysis.

The 3D images used allowed reformatting of images in any plane and confirm erosions and bone margins. 3D images have the ability to provide true volume of erosion as compared to 2D images, which use a slice thickness multiplication. The issue with this technique is that the anatomy is not densely sampled resulting in poorly represented regions between slices.

CT is known to be the gold standard for bone assessment. Recently manual segmentation of erosion on CT has been described (345), which may be beneficial in a cross-sectional setting but lack potential in a longitudinal environment due to radiation burden, lack of synovitis and BME assessments.

One other method of spectral MR analysis has been previously proposed but this can lack sensitivity for distinguishing between erosion and BME (323). Leung et al., proposed an automated method using image registration and segmentation propagation to assess volume change over time both global and local measure change (348).
In this work, the technique using bone mask extraction, image registration and bone centred transformation allows to accurately assess bones over time and can be used to manually outline erosions and potentially other disease activity measures like BME, though the latter was not assessed. This technique and accurate subtraction was also helped by the fact that the bridge device allowed similar wrist positioning longitudinally. A drawback of this method is that it is time consuming and thus can lack potential for widespread use. An automated version of this technique though has potential value with clinical PACS integration to assess visual changes over time.

The semi-automated technique is good in healthy and potentially early disease where there is not much marrow oedema or erosion, but this method, which uses thresholding fails in advanced disease, hence needs user interaction in assessment. In the pilot work, the semi-automated method was less labour intensive, much quicker and performed well in extracting bone volumes when evaluated against the manual technique. The promise shown by the semi-automated method is encouraging but still needs further testing in larger cohort of patients with different disease activity states. In summary, computerised bone segmentation tools including manual and semi-automated techniques are feasible and offer potential in volumetric bone analysis over time.
5 Results 3: 3 TESLA WRIST MRI IN ESTABLISHED RHEUMATOID ARTHRITIS AND EARLY METACARPAL BONE MINERAL DENSITY LOSS USING AUTOMATED DIGITAL X-RAY RADIOGRAMMETRY: A LONGITUDINAL ONE YEAR OBSERVATIONAL STUDY
5.1 Introduction:

Radiographic imaging (X-ray) has traditionally played a crucial role in diagnosis, as per 1987 ACR criteria (18) and in the follow-up of patients with rheumatoid arthritis (RA) (53, 54, 109). Evaluation of the extent and rate of structural damage involves standard hand and feet radiographs (104, 107) and the findings may inform treatment change and optimisation. The accepted method of joint damage assessment is hand and feet X-rays at annual or longer intervals. The time interval between assessments and insensitivity of radiographs to assess early joint damage is crucial as this is linked to loss of function and morbidity in the long term (55, 383, 384).

Radiographs identify periarticular osteopenia, erosions, joint space loss and changes of advanced disease including subluxation and fusion. The drawback with using X-rays is that it does not assess synovitis and bone marrow oedema (BME) (152). It is also well known that BME is an early disease activity measure that predicts future erosions (292). The time and costs involved in having repeated MRI as a follow-up imaging modality can limit its utility. Radiographs are cheaper, more readily available, quicker and routinely performed imaging in clinical practice in RA follow-up.

Osteoporosis in RA can manifest in two ways: generalized osteoporosis, which may be a result of immobility, disease related inflammatory process and treatments such as steroids; and periarticular osteoporosis/osteopenia, which is likely due to local release of inflammatory agents (74). Periarticular osteopenia is an early radiographic change in RA
It is known that early bone mineral density (BMD) loss is a predictor of diagnosis in RA in undifferentiated arthritis (386) and also a predictor of future joint damage (188). Periarticular osteopenia and bone erosions have been shown to correlate with disease activity (76). In RA the local and systemic bone loss is caused by increased osteoclastic activity (78). This increased activity also results in bone remodelling, erosion and periarticular bone loss (79). Osteoporosis in RA and various methods to measures BMD loss have been described in sections 1.3.3 and 1.4.2 respectively. The advantage of using DXR in hand BMD measurement compared to DXA is also explained in section 1.4.2.3.1.

DXR is a technique that provides estimation of BMD from geometric measurements conducted from single hand radiograph. Rosholm et al., described a new automated radiogrammetric method to assess bone mineral density loss (DXR-BMD) from single hand radiographs (103). This technique has been used to evaluate in early RA (188, 192, 200). The role of DXR in RA has been described earlier in section 1.4.2.3. It is known that DXR BMD loss increases with inflammation and increased disease activity (196, 197). The inflammation in bone is reflected as osteitis or as marrow oedema when imaged with MRI. Limited studies have assessed hand DXR BMD and MRI measures of disease activity over time (176, 198, 387).

5.2 Aim:

To evaluate the relationships between computerised automated early metacarpal bone mineral density loss and disease activity using high field strength 3T wrist MRI, and hand
and feet radiographic scores over a year in patients with established RA undergoing standard clinical care.

5.3 Methods:

The RA patient inclusion criteria, study timelines and assessments are described in Chapter 2 (section 2.2.1).

5.3.1 Imaging Analysis:

5.3.1.1 Visual Scoring:

Registered and aligned anonymised wrist MRI scans (n = 52) were scored using OMERACT RAMRIS (220), as described in section 2.2.4.1. X-rays in chronological order (n = 43) were scored using Van der Heijde modified Sharp (vdH Sharp) scoring (53, 117), as described in section 2.2.4.2.

5.3.1.2 Automated radiograph analysis:

DXR-online™, SECTRA, Sweden which uses a digital X-ray radiogrammetric method was used to calculate DXR-BMD (103). Using automated algorithms, the computer identifies second to fourth metacarpal diaphysis on digital hand radiographs and places regions of interest (ROI) for a length of 2 cm, 1.8 cm and 1.6 cm for 2nd, 3rd and 4th metacarpal
respectively (as shown in figure 25). Cortical thickness and bone width are calculated for each point and multiple such measurements made over the ROI. The final DXR-BMD is calculated automatically based on the formula (103): $\text{DXR-BMD} = c \times \text{VPA}_{mc} \times (1 - \text{P})$. Where $c$ is a constant, $\text{P}$ is an estimated porosity and $\text{VPA}$ is the weighted average of bone volume per projected area. The rate of change in DXR-BMD (RC-BMD) (mg/cm$^2$/month) was assessed. The automated radiogrammetric analysis using DXR-Online was performed by SECTRA, Sweden as part of academic collaboration (388). 9 patients’ radiographs were analysed over the year and 8 patients’ data were available at 12 weeks. 1 subject did not have MRI BME assessment at week 52; hence only 7 pairs of datasets with week 12 RC-BMD and week 52 MRI were available.

5.3.2 Statistics:

A repeated measure analysis of variance (ANOVA) was performed to evaluate radiographic and MRI scores, and disease activity measures over time, with bonferroni adjustment. Minimal detectable change at 1 year, $\text{MDC}_{95}$ (95% Confidence) was calculated (389). Interclass correlation coefficient (ICC) was used to assess total RAMRIS scores between two readers. A two way mixed model with consistency type was used. Normality was tested using Shapiro Wilks test. For normally distributed data Pearson correlation was used, otherwise spearman correlation was used, to evaluate statistical correlation between rate of change in bone mineral density (RC-BMD) and various MRI and X-ray scores. SPSS software was used for analysis.
Using automated algorithms, the computer identifies second to fourth metacarpal diaphysis on digital hand radiographs and places ROIs. Cortical thickness and bone width are
calculated for each point and multiple such measurements made over the ROI. The final DXR-BMD is calculated automatically based on a formula.

5.4 Results:

13 rheumatoid arthritis patients (10 female, 3 male), as per 1987 ACR criteria, were enrolled, 10 patients completed the study (9 female, 1 male) (1 RA subject could not complete study time points and dropped out after week 12. 1 RA subject developed superficial thrombophlebitis due to intravenous cannula at visit 1 and dropped out. 1 RA subject was claustrophobic and did not complete visit 1). Their ethnic background included 6 Caucasian, 2 Asian and 2 African origin subjects. Table 11 shows completed study group demographics.

The various disease modifying drugs (DMARDS) the patients were on, either as single drug or in combination, as part of their standard clinical care included Methotrexate (n = 9), Sulfasalazine (n = 3), Hydroxychloroquine (n = 3), Prednisolone (n = 3), and Interim Depomedrone intramuscular injection for flare up (n = 2).
### Table 11: Screening demographics of completed patient study group

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>St. dev</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>53.80</td>
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<td>38-70</td>
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<tr>
<td>BMI</td>
<td>25.90</td>
<td>4.23</td>
<td>19.8-31.8</td>
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<tr>
<td>Weight (Kg)</td>
<td>68.80</td>
<td>10.84</td>
<td>53-85</td>
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<tr>
<td>RA duration (months)</td>
<td>68.56</td>
<td>51.54</td>
<td>5-128</td>
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<tr>
<td>ESR</td>
<td>25.30</td>
<td>28.79</td>
<td>5-100</td>
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<tr>
<td>CRP</td>
<td>6.50</td>
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<td>TJC/28</td>
<td>5.20</td>
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<td>0-12</td>
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<td>SJC/28</td>
<td>5.70</td>
<td>3.97</td>
<td>1-13</td>
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<tr>
<td>Patient global VAS (mm)</td>
<td>19.60</td>
<td>12.33</td>
<td>1-32</td>
</tr>
<tr>
<td>DAS28</td>
<td>3.93</td>
<td>1.33</td>
<td>1.54-5.57</td>
</tr>
</tbody>
</table>

BMI-Body mass index, ESR-Erythrocyte sedimentation rate (mm/hour), CRP – C reactive protein (mg/L), TJC/28 – 28 tender joint count, SJC/28 – 28 swollen joint count, DAS 28 – Disease activity score based on 28 joints.

### 5.4.1 Disease activity measures:

The various disease activity measures (mean ± st. dev) are shown in table 12. The DAS 28 scores indicated overall moderate disease activity over the year, Day 1 (median: 4.22, range: 1.48 - 5.8), Week 4 (median: 3.47, range: 1.6 - 5.33), Week 12 (median: 4.0, range: 2.33 - 6.71), Week 24 (median: 3.9, range: 2.26 - 4.95) and Week 52 (median: 3.8, range: 1.55 - 7.2).
<table>
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<th></th>
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<th>Week 4</th>
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<td>st. dev</td>
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<td>st. dev</td>
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<td>ESR (mm)</td>
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<tr>
<td>CRP (mg/l)</td>
<td>5.7</td>
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<td>4.9</td>
<td>3.7</td>
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<tr>
<td>TJC/28</td>
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<td>4.2</td>
<td>3.7</td>
<td>3.6</td>
<td>6.2</td>
<td>6.1</td>
<td>4.8</td>
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<td>7.0</td>
<td>7.4</td>
<td></td>
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<tr>
<td>SJC/28</td>
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<td>4.5</td>
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<td>4.2</td>
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<td>2.3</td>
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<tr>
<td>SJC/66</td>
<td>4.6</td>
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<td>-</td>
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<td>8.2</td>
<td>2.4</td>
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<td>5.7</td>
<td>7.9</td>
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</tr>
<tr>
<td>Physician VAS (mm)</td>
<td>14.1</td>
<td>11.2</td>
<td>-</td>
<td>-</td>
<td>20.8</td>
<td>25.2</td>
<td>14.0</td>
<td>9.1</td>
<td>21.6</td>
<td>19.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMS (min)</td>
<td>13.0</td>
<td>22.1</td>
<td>-</td>
<td>-</td>
<td>36.8</td>
<td>79.0</td>
<td>11.9</td>
<td>18.6</td>
<td>29.3</td>
<td>39.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient global VAS (mm)</td>
<td>25.0</td>
<td>25.5</td>
<td>23.7</td>
<td>19.7</td>
<td>24.9</td>
<td>28.0</td>
<td>24.4</td>
<td>26.0</td>
<td>33.4</td>
<td>35.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient pain VAS (mm)</td>
<td>21.6</td>
<td>21.6</td>
<td>-</td>
<td>-</td>
<td>16.8</td>
<td>18.8</td>
<td>18.6</td>
<td>22.2</td>
<td>27.2</td>
<td>30.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAS 28</td>
<td>3.9</td>
<td>1.3</td>
<td>3.6</td>
<td>1.2</td>
<td>4.0</td>
<td>1.4</td>
<td>3.9</td>
<td>0.8</td>
<td>4.0</td>
<td>1.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAQ</td>
<td>1.0</td>
<td>0.8</td>
<td>-</td>
<td>-</td>
<td>0.8</td>
<td>0.7</td>
<td>0.8</td>
<td>0.7</td>
<td>0.9</td>
<td>0.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAF</td>
<td>23.3</td>
<td>12.6</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>21.8</td>
<td>14.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 12: Depicts various study disease activity measures over the year

No significant difference was seen in ESR, CRP, 28 Tender Joint Count (TJC/28), 28 Swollen joint count (SJC/28), 68 Tender Joint Count (TJC/68), physician VAS, EMS, Patient global VAS, DAS 28, HAQ, and MAF over time. Only 66 Swollen Joint Count (SJC/66) showed some significant change at week 24 but not at other time points (Table 13).
<table>
<thead>
<tr>
<th></th>
<th>Wilks’ Lambda</th>
<th>P value</th>
<th>Pairwise comparison over the year</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESR</td>
<td>0.60</td>
<td>0.65</td>
<td>Not significant</td>
</tr>
<tr>
<td>CRP</td>
<td>0.53</td>
<td>0.45</td>
<td>Not significant</td>
</tr>
<tr>
<td>TJC/28</td>
<td>0.64</td>
<td>0.63</td>
<td>Not significant</td>
</tr>
<tr>
<td>SJC/28</td>
<td>0.25</td>
<td>0.09</td>
<td>Not significant</td>
</tr>
<tr>
<td>TJC/68</td>
<td>0.95</td>
<td>0.95</td>
<td>Not significant</td>
</tr>
<tr>
<td>SJC/66</td>
<td>0.26</td>
<td>0.03</td>
<td>Day 1 - Week 24 (p = 0.03, 95% CI 0.15 - 4.95)</td>
</tr>
<tr>
<td>Physician VAS</td>
<td>0.84</td>
<td>0.78</td>
<td>Not significant</td>
</tr>
<tr>
<td>EMS</td>
<td>0.60</td>
<td>0.35</td>
<td>Not significant</td>
</tr>
<tr>
<td>Patient Global VAS</td>
<td>0.52</td>
<td>0.43</td>
<td>Not significant</td>
</tr>
<tr>
<td>DAS 28</td>
<td>0.69</td>
<td>0.77</td>
<td>Not significant</td>
</tr>
<tr>
<td>HAQ</td>
<td>0.73</td>
<td>0.58</td>
<td>Not significant</td>
</tr>
<tr>
<td>MAF</td>
<td>0.96</td>
<td>0.60</td>
<td>Not significant</td>
</tr>
</tbody>
</table>

Pairwise comparison was made between each time points over the year.

* p value < 0.05 was considered significant

*Table 13: Difference in disease activity measures over time*

### 5.4.2 RA MRI Scoring:

The MRI disease activity scores of this cohort of patients on standard routine treatment remained stable over the year. Mean change (% of maximum score) in synovitis, erosion and BME scores were -0.7 (-7.7%), 2.4 (1.6%) and 0.4 (0.8%) respectively at 1 year (table 14).

There was no significant change in MRI BME, synovitis, or erosion score over time. Figure 26, 27 and 28 depict box plot graph of BME, synovitis and MRI erosion respectively, range and mean over time.
Figure 29 shows individual patient MRI and radiographic scores over time. The minimal detectable change, MDC$_{95}$ (95% Confidence) at 1 year for MRI synovitis, erosion* and BME were 3.56, 16.51, 5.97 respectively; with standard error of measurement for synovitis: 1.28, erosion*: 5.95 and BME: 2.15. 1 subject with fused bones was excluded. No patients had 1 year change in synovitis or erosion score more than MDC$_{95}$. 1 patient (10%) had 1 year change in BME score more than MDC$_{95}$.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 4</th>
<th>Week 12</th>
<th>Week 24</th>
<th>Week 52</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synovitis (0-9)</td>
<td>5.8±1.9</td>
<td>5.8±2.7</td>
<td>5.3±2.9</td>
<td>5.2±1.8</td>
<td>5.1±1.7</td>
</tr>
<tr>
<td>Erosions* (0-150)</td>
<td>10.7±13.9</td>
<td>11.1±17.2</td>
<td>14.5±16.9</td>
<td>11.7±15.1</td>
<td>13.1±16.8</td>
</tr>
<tr>
<td>BME (0-45)</td>
<td>7.4±9.5</td>
<td>6.9±8.7</td>
<td>7.1±8.5</td>
<td>5.8±7.6</td>
<td>7.8±8.0</td>
</tr>
<tr>
<td>Total X-ray score (max 448)</td>
<td>33.6</td>
<td>-</td>
<td>34.4</td>
<td>34.7</td>
<td>35.4</td>
</tr>
</tbody>
</table>

* Erosions score excluded a patient with complete fused carpal joints. Mean ± St. dev. are shown.

*Table 14: MRI disease activity RAMRIS scores over 1 year*
**Figure 26:** Box plot graph showing BME score

1st and 3rd quartiles, with median and means plotted over time

**Figure 27:** Box plot graph showing synovitis score

1st and 3rd quartiles, with median and means plotted over time
Figure 28: Box plot graph showing MRI erosion scores

1st and 3rd quartiles, with median and means plotted over time
Figure 29: MRI and radiographic scores over time for all RA patients

Line graphs showing (a) MRI synovitis, (b) MRI erosion, (c) MRI BME, and (d) radiographic scores for all RA patients over time.
5.4.2.1 Inter class correlation for MRI scores:

There was good correlation amongst the two independent blinded scorers for MRI measures and inter class correlation coefficient (ICC) single measures for Erosions – 0.984, BME – 0.943, Synovitis – 0.657 (table 13).

<table>
<thead>
<tr>
<th>MRI disease Activity</th>
<th>Inter Class Correlation coefficient (ICC)</th>
<th>95% Confidence Interval</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synovitis</td>
<td>0.657</td>
<td>0.46</td>
<td>0.78</td>
</tr>
<tr>
<td>Erosions</td>
<td>0.984</td>
<td>0.97</td>
<td>0.99</td>
</tr>
<tr>
<td>BME</td>
<td>0.943</td>
<td>0.9</td>
<td>0.96</td>
</tr>
</tbody>
</table>

Table 15: Inter observer correlation results for RAMRIS scoring

5.4.2.2 Correlations of MRI disease activity measures:

5.4.2.2.1 Bone Marrow oedema score:

Bone marrow oedema (BME) scores correlated with synovitis scores at week 12 (p value = 0.001), and week 24 (p value = 0.0004). BME scores also correlated with erosions scores at week 24 (p value = 0.001), as shown in table 14 below. This is of note, as in our cohort on routine clinical care there was minimal increase in both BME and erosion scores over the year.
<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Week 4</th>
<th>Week 12</th>
<th>Week 24</th>
<th>Week 52</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corr</td>
<td>.60</td>
<td>.60</td>
<td>.89</td>
<td>.90</td>
<td>.68</td>
</tr>
<tr>
<td>p value</td>
<td>.06</td>
<td>.06</td>
<td>.001</td>
<td>.0004</td>
<td>.04</td>
</tr>
<tr>
<td>Corr</td>
<td>.60</td>
<td>.71</td>
<td>.74</td>
<td>.87</td>
<td>.80</td>
</tr>
<tr>
<td>p value</td>
<td>.03</td>
<td>.02</td>
<td>.02</td>
<td>.001</td>
<td>.009</td>
</tr>
</tbody>
</table>

**. Correlation (Corr) significant at the 0.01 level (2-tailed), adjusted for multiple comparisons

Table 16: Correlations of MRI BME with synovitis and erosions scores

5.4.2.2.2 MRI Erosion score:

In addition to correlating with BME scores at week 24, MRI erosion scores also correlated with synovitis at week 24 (\( \rho=0.837, \ p\text{ value}=0.003 \)).

5.4.2.2.3 MRI synovitis score:

At baseline synovitis score correlated with DAS 28 (\( r=0.83, \ p\text{ value}=0.003 \)).

5.4.3 Radiograph Analysis:

5.4.3.1 X-ray Scoring:

Total X-ray scores changed from baseline mean score of 33.6 to end of year score of 35.4 (out of a maximum score of 448), thereby an increase of 0.4%. This was not significant
(Wilks’ Lambda: 0.54, p value: 0.26). Figure 30 describes the box plot of total vdH Sharp score in patients, it is clearly seen that though the variation in total scores is large, a minimal increase is seen at 1 year. The MDC$_{95}$ for total X-ray score was 4.56 and standard error of measurement was 1.64. 1 patient (10%) had 1 year change in total X-ray score more than MDC$_{95}$.

![Figure 30: Box plot graph showing total X-ray scores](image)

1$^{st}$ and 3$^{rd}$ quartiles, with median and means plotted over time

4 out of 10 patients (40%) who completed the study showed no change in score. 2 patients (20%) had progression in hand scores, only due to erosions. One patient had an increase in hand erosion score by 1 at week 52 (total score 33 at baseline to 34 at week 52) and in another patient, hand erosion score increased by 3 (total score 51 at baseline to 54 at week 52).
1 patient (subject 2) progressed in hands and feet, total score increased from 38 at day 1 to 46 at week 52, figure 31. The increase is more heavily weighted on feet (6 score points). This patient showed progression throughout the year, at week 12 there was increased JSN in hands and feet which stabilised, but erosions in feet progressed.

![RA Subject 2](image)

*Figure 31: Bar chart shows progression in X-ray score over the year in RA subject 2*

3 patients progressed in the feet alone. One patient (subject 3) shows a small progression in radiographic scores over a year (28 at baseline to 31 at week 52). This is mainly due to increased changes in feet. At week 12 there was increase in feet JSN scores (11 to 12) which stabilised, with rise in feet erosion scores at week 24 & 52 (13 at baseline, 14 at week 24 and 15 at week 52), figure 32. Another patient (subject 8), also progressed in feet erosions over a year from 23 to 25, with total X-ray score from baseline to week 52 being 32 to 34.
There was no change in feet JSN. The third patient (subject 9) also progressed in feet erosions from a baseline score of 7 to 8 at week 12 which remained stable to the end, the total score being 60 at baseline and 61 at week 52.

Thus, we saw that 60% of the study patients progressed in radiographic scores, albeit with a small rise over a year (0.4%). 1 patient (10%) had change more than MDC_{95}. The majority (66%) of the patients that did progress showed progression in feet, which were largely due to erosions.

Figure 32: Bar chart shows progression in radiographic scores over a year in RA subject 3
5.4.3.2 Automated digital radiogrammetric analysis:

Rate of change of metacarpal bone mineral density (RC-BMD) (mg/cm\(^2\)/month) was similar over 12 weeks and 1 year, -0.48±1.5 and -0.55±1.2 (mean ± st. dev) respectively (table 17).

<table>
<thead>
<tr>
<th></th>
<th>Average</th>
<th>St. dev</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RC-BMD over 12 weeks [mg/cm(^2)/month]</strong></td>
<td>-0.48</td>
<td>1.5</td>
</tr>
<tr>
<td><strong>Average BMD change over 12 weeks [g/cm(^2)]</strong></td>
<td>-0.0008</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>RC-BMD over 1 year [mg/cm(^2)/month]</strong></td>
<td>-0.55</td>
<td>1.2</td>
</tr>
<tr>
<td><strong>Average BMD change over 1 year [g/cm(^2)]</strong></td>
<td>-0.006</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Table 17: DXR-BMD average and rate change (RC-BMD) over time

5.4.3.2.1 Metacarpal RC-BMD correlations with wrist MRI:

12 week RC-BMD showed no significant correlation with any 12 week and 24 week change scores.

12 week RC-BMD correlated with BME change (r = 0.78, p = 0.035) and ESR change (r = 0.91, p = 0.001) at 1 year. No correlation was seen with the change in DAS28, MRI erosion, synovitis, or X-ray scores.

Figure 33, shows 12 week RC-BMD and 12 week wrist BME change plotted for 8 RA patients over a year. Majority of patients with low RC-BMD had increased BME change and majority
of patients with increase in RC-BMD had reduced BME. Slight increase in RC-BMD was seen in 3 patients. On further evaluation, it was found that these subjects had a long duration of RA. One patient had fused carpal bones and may have had secondary sclerosis. In another subject (disease duration: 5 months), figure 19, there was rapid loss in RCBMD $-3.2 \text{mg/cm}^2/\text{month}$ and high BME score throughout the year (day 1, week 4, week 12, week 24, and week 52, with RAMRIS scores: 28, 26, 27, 22.5, and 23 out of 45). Hence, in spite of a small decrease in BME at 1 year, the bone loss continued as the overall burden of osteitis remained large.

*Figure 33: 12 week RC-BMD change mapped with 12 week wrist BME change for RA patients*
5.5 Discussion:

Plain radiographs form a routine and widely used way of assessing RA joint damage (107, 109). Application of newer imaging modalities, like MRI plays a more crucial role in identifying early changes, like early erosions, synovitis and BME, that lead to radiographic damage and morbidity in the long term. There has been an increasing trend towards using these in clinical trials with comparison made to changes on radiographs (110, 111, 214).

In RA, inflammation in a joint is a predictor of future damage in that joint (56). Joint swelling and tenderness is a component of DAS assessment (45) and is a clinical indicator of synovitis and inflammation in that joint. In this study an average of moderate (390) DAS 28 was seen throughout the year, but no significant change was seen in any disease activity or MRI measures over the year.

There were good correlations between various MRI disease activity measures over the year. Synovitis correlated with BME at week 12 and 24. BME has been well described to be a precursor for future erosions (292). Mc Queen et al., have described the association of baseline bone oedema to erosions at 1 year (110). In this study there was association between BME and MRI erosions. Even though no significant disease activity change was seen in this cohort of patients on routine clinical care over the year, there was a very small increase in MRI erosions (1.6%), BME (0.8%) and radiographic scores (0.4%). An inference could be made that despite being on standard clinical care patients with moderate disease activity demonstrate a small progression in erosions. It has been well described in literature
that patients in clinical remission can manifest persisting joint inflammation on histology and imaging (61). 60% of the study patients progressed in radiographic scores, albeit a small rise over a year (0.4%). 66% of the patients that had radiographic progression showed progression in feet, which were largely due to erosions. This is similar to what has been described previously (107, 115). Only 1 patient (10%) had change in radiographic scores more than the minimal detectable change.

Figure 34 shows a study RA patient with MRI erosions in distal ulna, scaphoid, triquetrum, and hamate. There is BME in triquetrum at Day1 with an increase in erosion at week 52. A small increase in BME in distal ulna and lunate over the year is also noted. This small increase in BME would still score the same score when using RAMRIS, but as we know BME is a precursor for erosions. Hence, early measures which can correlate with BME would be of value in predicting disease progression.
Figure 34: MRI disease activity changes from Day 1 to week 52 in RA subject 9

MRI shows erosions in distal ulna (orange arrow), scaphoid, triquetrum (blue arrow), and hamate (green arrow). There is BME in triquetrum at Day 1 (white arrow) with an increase in erosion at week 52 (blue arrow). A small increase in BME in distal ulna (white circle) and lunate over the year is also noted. Marked synovitis (yellow star) is also seen over the year.

The early changes on radiographs, i.e. bone mineral density loss are quite commonly seen in RA. Loss of metacarpal bone mineral density is known to predict RA development in recent onset arthritis (386). It is also described as an independent predictor of future damage in RA patients, and potentially an important clinical investigation tool (190, 391).

Inflammatory cytokines such as TNF and IL6 have been linked with increased osteoclastic activity, which have been associated with alteration of bone metabolism in early RA (392, 393). Therapies inhibiting inflammatory cytokines have shown to reduce bone loss in RA (203). It has been recently described that Infliximab, an anti-TNF, agent improves bone
mineral density and metabolism in rheumatoid arthritis (394). Bone marrow oedema in RA indicates the presence of active inflammation and osteitis, which is also associated with inflammatory cytokines (395). This has been demonstrated with histological confirmation (284), and have shown improvement with anti-TNF treatment (279).

In this study cohort, significant correlation was seen between early (12 week) RC-BMD and 1 year change in wrist BME. This could potentially indicate that DXR-BMD change possibly mirrors osteitis seen on MRI macroscopically to already known microscopic and cytokine associations.

Stewart et al., revealed that 1 year change in DXR-BMD in RA patients predicts who will become erosive at 4 years (181). In early phase clinical trials early imaging predictive biomarkers are required, and thus DXR-BMD offers potential. In the present study even earlier DXR-BMD change was evaluated, i.e. over 3 months. This correlated with BME at 1 year, which is known to predict future radiographic joint damage in RA (198, 292, 396). Also of note was that the RC-BMD change over 12 weeks and 1 year was similar, though there was increased loss at 1 year (table 17). Hence, this early measure could enable clinicians to use a readily available modality to follow-up patients.

In a recent study, Boyesen et al., described that 3 months hand bone loss and baseline MRI predict 1 year MRI erosion in early RA (387). Large 3 month DXR bone loss has also been seen in patients with MRI erosion progression (198). No significant correlation was seen in this cohort between 3 month RC-BMD and 1 year MRI/radiographic erosion scores. There could be several reasons for this; firstly, the patients were mostly with established RA on
standard combination of disease modifying therapy. Most studies have looked at early RA or undifferentiated arthritis and these cohorts were often selected for poor prognostic factors and thus exhibited a much faster average rate of structural damage. Secondly, in patients with established RA on standard clinical care these findings could reflect a slower kinetic in the appearance of MRI/radiographic erosion than that of RC-BMD change reflecting more rapid periarticular bone loss and thus generating the hypothesis that RC-BMD may be a sensitive and early structural prognostic marker in RA follow-up.

3T wrist MRI was used in this study, it is known that at higher field strengths there is better signal to noise ratio and hence better resolution (311, 314, 315, 318). This is crucial when imaging small joints, namely wrists, which are commonly involved in RA. Good ICC was seen between two independent scorers for the MRI scans; similar to what has been previously described on other imaging platforms (334).

It was noted that stable patients on routine clinical care still have very minimal increase (% of maximum score) in MRI erosion (1.6%) and BME (0.8%), X-ray radiographic (0.4%) scores. This would be within the realms of stable disease on visual inspection. But even on this small amount of change there were correlations between early RC-BMD and 1 year wrist BME. Thus, offering promising potential as an early follow-up imaging tool in management of RA patients.

It is well known that oral steroids reduce bone mineral density. In this pilot study, of the 8 patients with RC-BMD results at week 12, only 2 patients were on regular oral prednisolone,
out of which 1 subject showed increase in RC-BMD. Hence, the results observed in the cohort as a whole for change in RC-BMD over time could not be accounted by the use of steroid therapy. A limitation of the current pilot study is the small cohort size. Nevertheless, this is to the authors knowledge the only study to evaluate metacarpal RC-BMD using DXR and 3T wrist MRI in a longitudinal fashion in established RA patients with wide range of disease duration.

In conclusion, it has been shown in this pilot study that early 12 week metacarpal RC-BMD change correlates with 1 year wrist BME change. BME is well known to be a predictor of future erosions. However, in this cohort no correlations were seen between RC-BMD and the progression of radiologic damage in the form of erosions at 1 year. This raises the possibility that in patients with established RA on standardised treatment and a low annualized rate of radiographic progression, DXR may offer a tool as an early indicator of insidious damage progression over the longer term and possibly also of functional loss. These findings and the generated hypothesis need to be evaluated in a larger cohort of patients.
6 RESULTS 4: EVALUATING AUTOMATED DYNAMIC CONTRAST ENHANCED WRIST 3 TESLA MRI: A 1 YEAR LONGITUDINAL STUDY IN HEALTHY VOLUNTEERS AND RHEUMATOID PATIENTS
6.1 Introduction:

Treatment of RA patients has been improved with introduction of biologic agents, which target specific cytokines or cells involved in the disease process (397). Nonetheless, most patients achieve only partial therapeutic response and many do not respond at all. Many new therapeutic agents are being investigated in clinical trials with the aim to improve patient outcomes and limit joint damage (397). In order to expedite early phase assessment of efficacy for inflammation reduction and disease modification, there is demand for optimisation of imaging techniques, image reading and quantification of follow-up for patients.

Dynamic contrast enhancement (DCE)-MRI is considered a valuable modality for quantitative assessment of the inflammed synovium in RA (356). DCE-MRI provides important information about the time dependent tissue contrast uptake, allowing to quantify regional activity and synovitis change (276, 349, 356, 358, 359) and BME (362) which have shown high predictive value in future disease progression (351, 363).

The MRI semi-quantitative scoring system (OMERACT RAMRIS) is the current widely used method of assessing synovitis (220). These synovial scores have been validated and widely used in RA clinical trials but are limited to defined areas in the wrist (distal radioulnar, radiocarpal and intercarpal-carpometacarpal joints) and provide a scale (0-3) of activity. They also require trained readers and provide rigid scores, capturing changes of 30% with
each score. They lack ability to detect quantification of perfusion measures and small changes in synovitis (329, 350, 351).

It is known from imaging studies that it is crucial to measure even slightest variation in patients’ condition through synovial perfusion and quantitative measures, which are of prognostic value (62, 398). Patients in remission are known to have a low grade of synovial disease activity (62) and it would be important to measure this in an objective manner and preferably on a continuous scale.

A computer aided technique has been described by Kubassova et al (329, 367, 368) which corrects for motion correction and uses automated voxel-by-voxel parametric map based analysis method of signal intensity vs time curves (329). It allows for continuous assessment of synovial changes; with automation of ‘reading’ and computer guidance in image analysis it does not require an observer to undergo extensive training. DCE-MRI analysis tools and high field strength MRI is anticipated to have potential utility in the setting of early phase clinical trials in inflammatory arthritis where the ability to quantify small changes in disease activity and structural damage progression over time is crucial to evaluate any therapeutic benefit of drug intervention.

In studies it is assumed that any changes seen in MRI and DCE-MRI can be entirely attributed to treatment, whereas it is known that MRI and DCE-MRI can have inherited variability due to various factors, such as reduction in image quality due to motion artefact, hardware instability or change in patient condition, amongst others. Therefore, any quantitative parameters extracted from DCE-MRI should be adjusted for these factors.
There are few studies evaluating MR imaging measures in a healthy population (308, 372, 373, 399-405). Previously, semi-quantitative visual RAMRIS scoring method (220) have been used to analyse healthy volunteers (372, 373, 399, 401, 406).

Prior to using DCE-MRI method in longitudinal studies it is important to evaluate what is the change/variability in the DCE-MRI parameters over time in healthy subjects where no change is expected but some enhancement can be seen (inherent/background change) and in RA patients on routine clinical care. This validation would be useful to define cut off levels for treatment strategies. The focus of this study was to validate the background change occurring over time as imaged with DCE-MRI to allow reader to make a judgement on what changes can be truly attributed to treatment effect. The study aimed at evaluating the new computerised DCE-MRI methods in healthy cohorts and RA patients on routine clinical care over a year.

To the authors knowledge this was the first longitudinal study to explore 3T wrist DCE-MRI change over 1 year in healthy volunteers and rheumatoid patients using automated and objective software tools. This validation was crucial if this technique was to be incorporated in drug trial design or research studies focusing on early detection and treatment effect assessment.
6.2 Methods:

Study patient cohort, timelines and assessments are described in Chapter 2 (section 2.2). 13 rheumatoid patients and 10 healthy subjects were recruited. DCE-MRI data from 10 rheumatoid and 7 healthy subjects were available for analysis.

6.2.1 Data Analysis:

DCE-MRI data was analysed using Dynamika software (Image Analysis, UK). The software allowed for motion correction based on an integrated motion correction algorithm (329). Using motion correction significantly impacts both the signal to noise as well as the accuracy of quantitative analysis through reduction of the artefactual enhancement (378). Quantification of wrist DCE-MRI data from each time point was performed, by the author, using parametric maps which are based on a fully-automated voxel-by-voxel analysis of signal intensity vs. time curves incorporated in the software. The pattern of each signal intensity vs. time curve was assigned a colour on gadolinium maps – (1) No contrast agent uptake, which might indicate healthy tissue. (2) Persistent enhancement, which shows tissues that exhibit baseline and wash-in phase, but do not reach an intensity plateau during the acquisition time interval. (3) Plateau, which shows tissues which exhibit baseline, wash-in, and intensity plateau phases. These tissues were normally located within disease affected areas. (4) Wash-out, for tissues exhibiting baseline, wash-in, plateau and wash-out phases. They were normally located within severely inflammed areas or blood vessels.
$N_{total}, N_{plateau}, N_{washout}$ represent the total number of enhancing voxels, and voxels with plateau and washout pattern respectively, and $N_{plw} = N_{plateau} + N_{washout}$. Parameters of maximum enhancement ($ME$) – which is the variation in signal intensity from the baseline, initial rate of enhancement ($IRE$) – which shows the slope of the signal intensity vs. time curve during contrast uptake, and time of onset of enhancement ($T_{onset}$) - which is the time when contrast uptake starts, were extracted automatically (329) and are shown as colour image iMaps for Gadolinium (Gd), ME, IRE, and $T_{onset}$, figure 35a-d for a healthy subject and figure 36a-d for RA patient. ME shows the variation (%) of the intensity from baseline, where 1 is the baseline intensity; IRE is the slope of the signal intensity vs. time curves during the contrast agent uptake, %/sec. $T_{onset}$ (sec) is the time when the contrast uptake starts (Figure 39). All these measurements were performed in a fully automated manner. The maps were used as a reference to draw ROI around the wrist and any enhancing synovium.

The following analysis methods were undertaken:

(1) The whole wrist including the muscles, vessels, bones and synovium, in all temporal slices that included the carpal bones (Whole wrist);

Using visual guidance, the author drew several regions of interest (ROI) positioned as follows:

(2) Around the carpal bones to exclude the vessels and to include both radio-carpal and ulna-carpal, intercarpal and carpometacarpal joints (Rough Wrist ROI).

(3) Around a specific synovial enhancement within the carpal bones (Precise Wrist ROI).
A ROI was placed on the slice with the maximum synovial enhancement and propagated over adjacent slices to measure the average of 3 slices. Normalised persistent, plateau and washout were voxels with the persistent, plateau and washout pattern of enhancement as % of the total ROI size. $ME_{\text{mean}}$, $ME_{\text{st. dev}}$, $IRE_{\text{mean}}$ and $IRE_{\text{st. dev}}$ were the mean and st. dev values of maximum enhancement (ME) and initial rate of enhancement (IRE).
Figure 35: Parametric maps for (a) Gd, (b) ME, (c) IRE, and (d) $T_{\text{onset}}$ for a healthy subject.

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Figure 36: Parametric reference maps for (a) Gd, (b) ME, (c) IRE, and (d) $T_{onset}$ for a rheumatoid subject.
Figure 37 (A-B) illustrates parametric maps of Gd and IRE acquired from the wrist joint of a healthy subject. There is normal tissue and muscle enhancement following the use of contrast with no visible enhancement around the joints. Figure 37 (C-D) shows maps of Gd and IRE acquired from a RA patient with enhancement in the wrist. In the Gd maps, blue represents persisting, green represents plateau and red areas show washout pattern. Bright white-yellow colours in the map of IRE correspond to the tissue with more pronounced synovial inflammation; darker red colour - with lesser disease activity. The colour maps were superimposed on the anatomical image. ME colour maps range from black to white, with black being no enhancement and white, maximum enhancement. Red and yellow are in between.
Figure 37: Parametric maps for a healthy subject and an active RA patient

Parametric maps of healthy (A-B) and RA subjects (C-D). In the Gd maps (A) and (C), blue represents persisting, green represents plateau and red areas show washout pattern. Bright white-yellow colours in the map of IRE (B) and (D) correspond to the tissue with more pronounced synovial inflammation; darker red colour - with lesser disease activity. In the healthy no enhancement is seen in the joint, whereas there is marked uptake in the RA patients.

Figure 38 shows signal intensity vs. time curves, (a) ROI drawn around the radial artery shows a signal intensity curve with rapid peak as contrast enters the wrist followed by
gradual washout. (b)rough wrist ROI shows no enhancing synovium and the signal intensity curve is erratic, this is likely to be due to background noise in this healthy subject. Figure 39 shows signal intensity vs. time curves with rapid peak as contrast enters the wrist followed by plateau phase. This patient had early RA (disease duration 5 months), moderate disease activity with DAS 28: 4.49 and high ME: 1.848.

Figure 38: Shows signal intensity graphs comparing ROI around artery and healthy wrist

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(a) ROI drawn around the radial artery shows a signal intensity curve with rapid peak as contrast enters the wrist followed by gradual washout. (b) rough wrist ROI shows no
enhancing synovium and the signal intensity curve is erratic, this is likely to be due to background noise in this healthy subject.

Figure 39: Signal intensity vs time curve for ROI drawn around synovitis in a RA wrist

The curve shows rapid peak followed by plateau phase in an active RA patient. Baseline is the signal intensity before contrast reaches the wrist; $T_{onset}$ (sec) is the time when the contrast uptake starts. IRE is the slope of the signal intensity vs. time curves during the contrast agent uptake, %/sec. ME shows the variation (%) of the intensity from baseline, where 1 is the baseline intensity.

DCE-MRI analysis was done by the author in a prospective manner and was aware of the condition of the subject, i.e. patient or healthy. 26 DCE-MRI images for healthy subjects were analysed, 2 healthy subjects were excluded as they only had the Day 1 scan and no follow-up, and 2 subjects did not have the week 52 scan. 47 rheumatoid patient DCE-MRI images were analysed. 1 patient did not undergo the week 12 scan and for 2 patients the week 52 DCE-MRI scan could not be obtained due to scanner issues.
6.2.2 Statistics:

Spearman correlation (rho - ρ) was used to evaluate synovitis, DAS 28 and DCE-MRI measures over time. P values <0.05 (2 tailed) and P value < 0.01* for multiple comparisons have been shown. Mann Whitney test was used to compare healthy and rheumatoid patient results. SPSS 18 software was used for statistical analysis.

6.3 Results:

6.3.1 Healthy Subjects:

10 Healthy subjects enrolled (3 male and 7 female), 7 completed the study (3 male and 4 females, mean age: 30.7 years, age range: 24 - 40 years). In total 28 MRI scans were performed; 9 subjects completed baseline, 7 subjects completed week 12, 24 visits and 2 subjects dropped out at week 52 due to pregnancy and a surgery. 1 subject had a vasovagal after venous cannulation on Day 1 and dropped out, 2 subjects withdrew after Day 1, and 2 subjects did not have their week 52 MRI as one had metal work from recent surgery and the other was pregnant.

6.3.1.1 X-ray Scoring:

6 subjects had baseline and week 52 X-rays of hand and feet performed. All except 2 subjects had a vdB Sharp score of 0. One subject had a joint space narrowing (JSN) score of
2 for hands and the other subject a score of 6 for JSN of feet. These remained unchanged over a year, and likely represent old changes of unknown significance. No subject had any radiographic erosion and all scored 0. Thus, as expected there were no erosions or radiographic change in healthy subjects over a year.

6.3.1.2 MRI Scoring:

The average±standard deviation total OMERACT RAMRIS scores at baseline, week 12, week 24 and week 52 for synovitis (possible range 0-9) were 3.5 ± 2.6, 3.3 ± 1.6, 3.7 ± 2.0, and 4.5 ± 1.7; for erosions (possible range 0-150) were 0.8 ± 1.3, 0.4 ± 0.7, 0.4 ± 0.7, and 1.4 ± 1.9 and for BME (possible range 0-45) were 0.6 ± 0.7, 0.2 ± 0.5, 0.2 ± 0.4, and 0.3 ± 0.6 respectively (table 18).

No MRI erosions were scored in any MCP base or pisiform by either scorer. Erosions in both the lunate and distal ulna was scored by both scorers independently at baseline but not at future timepoints in one subject each. In one subject the triquetrum was scored for erosion by both scorers at week 12 and 52 but not others. In 6 subjects, atleast at one time point, an erosion was scored by either scorer. In 2 subjects no erosion was scored by either scorer over a year. In summary, no erosions were scored consistently over the year.

Scoring of healthy and RA subjects were done in a blinded fashion and in a random order. Thus the two independent radiologists were not aware as to the disease status of the subject. When asked to define if the images were from healthy or RA subjects based on
RAMRIS, the two independent radiologists felt that 4 out of 28 MRI scans showed signs of rheumatoid arthritis, likely based on synovitis and oedema scores, giving RAMRIS scoring a specificity of 85.7%.

Only the lunate in one subject was consistently scored for BME over the year. Thus, BME can rarely be seen in healthy subjects. It was seen that low scoring and BME can be seen in healthy subjects and there is also synovial uptake, but these levels are much lower than that what is seen in rheumatoid patients. It is worth noting that no radiographic erosions were seen in healthy subjects.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 4</th>
<th>Week 12</th>
<th>Week 24</th>
<th>Week 52</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Healthy</td>
<td>Patients</td>
<td>Healthy</td>
<td>Patients</td>
<td>Healthy</td>
</tr>
<tr>
<td><strong>Synovitis</strong></td>
<td>3.5±2.6</td>
<td>5.8±1.9</td>
<td>-</td>
<td>5.8±2.7</td>
<td>3.3±1.6</td>
</tr>
<tr>
<td><strong>(0-9)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Erosions</strong></td>
<td>0.8±1.3</td>
<td>10.7±13.9</td>
<td>-</td>
<td>11.1±17.2</td>
<td>0.4±0.7</td>
</tr>
<tr>
<td><strong>(0-150)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BME</strong></td>
<td>0.6±0.7</td>
<td>7.4±9.5</td>
<td>-</td>
<td>6.9±8.7</td>
<td>0.2±0.5</td>
</tr>
<tr>
<td><strong>(0-45)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total X-ray</strong></td>
<td>8</td>
<td>33.6</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>(max 448)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* One RA patient had fused joints so not included. Results in mean ± std.

**Table 18: Compares MRI and radiographic scores for healthy subjects and RA patients over 1 year**
DCE-MRI data was quantified by measuring the mean and standard deviation of the imaging based biomarkers. In ‘whole wrist’ assessments, parameters changed significantly over the year due to inclusion of enhancing muscle and blood vessels (table 19). Mean values from baseline - week 52 were: $N_{\text{total}}$ (1878.14 - 2295), $N_{\text{persistent}}$ (69.71 - 56), $N_{\text{plateau}}$ (1479.85 - 1728.8), $N_{\text{washout}}$ (327.14 - 509.2), $N_{\text{plw}}$ (1807.85 - 2238.4), $\text{ME}_{\text{mean}}$ (1.38 - 1.34), $\text{IRE}_{\text{mean}}$ (0.008 - 0.008). The maximum variation (mean±st. dev) in these measures from baseline were: $N_{\text{total}}$ (482.2±410.8 at week 52), $N_{\text{persistent}}$ (22.2±43.9 at week 12), $N_{\text{plateau}}$ (291±421.9 at week 52), $N_{\text{washout}}$ (199±173.8 at week 52), $N_{\text{plw}}$ (489.4±445.9 at week 52), $\text{ME}_{\text{mean}}$ (-0.08±0.1 at week 24), $\text{IRE}_{\text{mean}}$ (-0.002±0.005 at week 12 and 24).
<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Wk12</th>
<th>Wk24</th>
<th>Wk52</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Whole Wrist</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( N_{\text{total}} )</td>
<td>1878.14</td>
<td>2100.42</td>
<td>1992.28</td>
<td>2295</td>
</tr>
<tr>
<td>( \mu )</td>
<td>773.46</td>
<td>820.13</td>
<td>673.61</td>
<td>858.71</td>
</tr>
<tr>
<td>( \sigma )</td>
<td>2100.42</td>
<td>820.13</td>
<td>673.61</td>
<td>858.71</td>
</tr>
<tr>
<td>( N_{\text{persistent}} )</td>
<td>69.71</td>
<td>92</td>
<td>70.85</td>
<td>56</td>
</tr>
<tr>
<td>( \mu )</td>
<td>24.66</td>
<td>30.66</td>
<td>28.95</td>
<td>34.39</td>
</tr>
<tr>
<td>( \sigma )</td>
<td>92</td>
<td>30.66</td>
<td>28.95</td>
<td>34.39</td>
</tr>
<tr>
<td>( N_{\text{plateau}} )</td>
<td>1479.85</td>
<td>1582.14</td>
<td>1635.85</td>
<td>1728.8</td>
</tr>
<tr>
<td>( \mu )</td>
<td>713.13</td>
<td>665.46</td>
<td>552.4</td>
<td>638.65</td>
</tr>
<tr>
<td>( \sigma )</td>
<td>1582.14</td>
<td>665.46</td>
<td>552.4</td>
<td>638.65</td>
</tr>
<tr>
<td>( N_{\text{wash-out}} )</td>
<td>327.14</td>
<td>425</td>
<td>284.42</td>
<td>509.2</td>
</tr>
<tr>
<td>( \mu )</td>
<td>74.35</td>
<td>226.81</td>
<td>202.21</td>
<td>223.1</td>
</tr>
<tr>
<td>( \sigma )</td>
<td>425</td>
<td>226.81</td>
<td>202.21</td>
<td>223.1</td>
</tr>
<tr>
<td>( N_{\text{plateau}}+N_{\text{wash-out}} )</td>
<td>1807.85</td>
<td>2008</td>
<td>1920.71</td>
<td>2238.4</td>
</tr>
<tr>
<td>( \mu )</td>
<td>773.11</td>
<td>841.14</td>
<td>691.58</td>
<td>843.53</td>
</tr>
<tr>
<td>( \sigma )</td>
<td>2008</td>
<td>841.14</td>
<td>691.58</td>
<td>843.53</td>
</tr>
<tr>
<td><strong>ME\text{max}</strong></td>
<td>6.23</td>
<td>4.48</td>
<td>4.39</td>
<td>4.67</td>
</tr>
<tr>
<td><strong>ME\text{mean}</strong></td>
<td>1.38</td>
<td>1.32</td>
<td>1.3</td>
<td>1.34</td>
</tr>
<tr>
<td><strong>IRE\text{max}</strong></td>
<td>0.26</td>
<td>0.16</td>
<td>0.15</td>
<td>0.23</td>
</tr>
<tr>
<td><strong>IRE\text{mean}</strong></td>
<td>0.008</td>
<td>0.006</td>
<td>0.002</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Mean (\( \mu \)) and standard deviation (\( \sigma \)). Reproduced with permission from Rastogi et al and Elsevier

Table 19: Quantitative parameters for the healthy ‘whole’ wrist analysis over the year

Once a ‘rough ROI’ was placed to exclude the highly variable muscle tissue and blood vessels, the mean and standard deviation of all parameters were stable (table 20). Specifically, at baseline, the mean±st. dev of ME and IRE were 1.2±0.07 and 0.001±0.0008 and the changes over the year did not exceed 0.04. The mean±st. dev changes for parameters over the year (baseline, week 12, 24, 52) were as follows: ME\text{mean} (1.26±0.07, 1.25±0.06, 1.27±0.11, 1.29±0.08), IRE\text{mean} (0.001±0.0008, 0.001±0.0005, 0.002±0.001, 0.002±0.001). The maximum variation (mean±st. dev) in these measures from baseline were: ME\text{mean} (0.04±0.02 at week 52), IRE\text{mean} (0.0006±0.0009 at week 52), Normalised
persistent (-0.42±0.84 at week 24), Normalised plateau (3.79±3.45 at week 52) and Normalised wash-out (1.95±0.9 at week 52).

<table>
<thead>
<tr>
<th>Rough Wrist ROI</th>
<th>Baseline</th>
<th>WK 12</th>
<th>WK 24</th>
<th>WK 52</th>
</tr>
</thead>
<tbody>
<tr>
<td>ME_{mean}</td>
<td>1.26</td>
<td>1.25</td>
<td>1.27</td>
<td>1.29</td>
</tr>
<tr>
<td>ME_{st. dev.}</td>
<td>0.10</td>
<td>0.1</td>
<td>0.13</td>
<td>0.12</td>
</tr>
<tr>
<td>IRE_{mean}</td>
<td>0.001</td>
<td>0.001</td>
<td>0.002</td>
<td>0.002</td>
</tr>
<tr>
<td>IRE_{st. dev.}</td>
<td>0.0009</td>
<td>0.001</td>
<td>0.002</td>
<td>0.002</td>
</tr>
<tr>
<td>Normalised Persistent</td>
<td>0.88</td>
<td>1.08</td>
<td>0.45</td>
<td>0.59</td>
</tr>
<tr>
<td>Normalised Plateau</td>
<td>11.28</td>
<td>12.22</td>
<td>11.75</td>
<td>13.37</td>
</tr>
<tr>
<td>Normalised Wash-out</td>
<td>1.23</td>
<td>2.1</td>
<td>0.85</td>
<td>3.01</td>
</tr>
</tbody>
</table>

Mean (μ) and standard deviation (σ). Reproduced with permission from Rastogi et al and Elsevier

Table 20: Quantitative parameters for the healthy ‘rough’ ROI analysis over the year

Placement of a precise ROI demonstrated similarly stable results (table 21). The mean±st. dev changes for parameters over the year (baseline, week 12, 24, 52) were as follows: ME_{mean} (1.28±0.09, 1.26±0.07, 1.32±0.17, 1.32±0.12), IRE_{mean} (0.001±0.0008, 0.002±0.001, 0.002±0.002, 0.002±0.001). The maximum variation (mean±st. dev) in these measures from
baseline were: $\text{ME}_{\text{mean}}$ (0.04±0.04 at week 52), $\text{IRE}_{\text{mean}}$ (0.0008±0.001 at week 24 and 52), Normalised persistent (-0.82±1.58 at week 52), Normalised plateau (-4.27±13.82 at week 12) and Normalised wash-out (5.81±7.47 at week 52).

<table>
<thead>
<tr>
<th>Precise Wrist ROI</th>
<th>Baseline</th>
<th>WK 12</th>
<th>WK 24</th>
<th>WK 52</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mu$</td>
<td>1.28</td>
<td>1.26</td>
<td>1.32</td>
<td>1.32</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>0.09</td>
<td>0.07</td>
<td>0.17</td>
<td>0.12</td>
</tr>
<tr>
<td>$\mu$</td>
<td>0.10</td>
<td>0.11</td>
<td>0.14</td>
<td>0.13</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>0.07</td>
<td>0.08</td>
<td>0.12</td>
<td>0.1</td>
</tr>
<tr>
<td>$\mu$</td>
<td>0.001</td>
<td>0.002</td>
<td>0.002</td>
<td>0.002</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>0.0008</td>
<td>0.001</td>
<td>0.002</td>
<td>0.002</td>
</tr>
<tr>
<td>$\mu$</td>
<td>0.0009</td>
<td>0.002</td>
<td>0.002</td>
<td>0.002</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>0.0004</td>
<td>0.002</td>
<td>0.002</td>
<td>0.002</td>
</tr>
<tr>
<td>$\mu$</td>
<td>1.57</td>
<td>1.36</td>
<td>1.03</td>
<td>0.92</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>1.66</td>
<td>1.42</td>
<td>1.16</td>
<td>0.99</td>
</tr>
<tr>
<td>$\mu$</td>
<td>22.43</td>
<td>18.16</td>
<td>19.37</td>
<td>24.49</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>21.22</td>
<td>13.2</td>
<td>16.8</td>
<td>14.47</td>
</tr>
<tr>
<td>$\mu$</td>
<td>1.72</td>
<td>3.2</td>
<td>1.1</td>
<td>7.62</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>1.57</td>
<td>2.75</td>
<td>1.22</td>
<td>6.66</td>
</tr>
</tbody>
</table>

Mean ($\mu$) and standard deviation ($\sigma$). Reproduced with permission from Rastogi et al and Elsevier

*Table 21: Quantitative parameters for the healthy ‘precise’ ROI analysis over the year*

### 6.3.1.4 Correlations between healthy subject baseline synovitis score and DCE-MRI parameters:

The following correlations were seen:
In whole wrist analysis with $N_{\text{total}} \rho = 0.793 \ (P=0.033)$, $N_{\text{plateau}} \rho = 0.793 \ (P=0.033)$, $N_{\text{washout}} \rho = 0.757 \ (P=0.048)$, $N_{\text{plateau}}+N_{\text{washout}} \rho = 0.793 \ (P=0.033)$.

In ‘rough’ wrist ROI analysis, with $\text{ME}_{\text{mean}} \rho = 0.865 \ (P=0.011)$, $\text{ME}_{\text{st.dev}} \rho = 0.919^* \ (P=0.003)$, $\text{IRE}_{\text{st.dev}} \rho = 0.908^* \ (P=0.004)$, normalised plateau $\rho = 0.955^* \ (P=0.0008)$, normalised washout $\rho = 0.883^* \ (P=0.008)$.

In ‘precise’ ROI analysis, with $\text{ME}_{\text{mean}} \rho = 0.955^* \ (P=0.0008)$, $\text{ME}_{\text{st.dev}} \rho = 0.847 \ (P=0.016)$.

6.3.2 Rheumatoid patients:

6.3.2.1 RA X-ray Scoring:

Total X-ray scores changed from a baseline mean score of 33.6 to a year end score of 35.4. Results are described in detail in section 5.4.3.1.

6.3.2.2 RA MRI Scoring:

The MRI disease activity scores of the study patients on standard routine treatment over the year remained stable. Mean changes (%) in synovitis, erosion and BME scores were -0.7 (-7.7%), 2.4 (1.6%) and 0.4 (0.8%) respectively over the year. Table 18 compares results for healthy and rheumatoid patients. Detailed results have been described in section 5.4.2.
6.3.2.3 RA patients DCE-MRI analysis:

In RA patients ‘whole wrist’ assessment, as seen in healthy subjects, parameters changed significantly over the year due to inclusion of enhancing muscle and blood vessels (table 22). Mean values from baseline - week 52 were: $N_{total}$ (1846.9 – 2024.6), $N_{persistent}$ (48.9 – 75.1), $N_{plateau}$ (1405.7 - 1454), $N_{washout}$ (391.4 – 494.6), $N_{plw}$ (1797.6 – 1949.1), ME$_{mean}$ (1.43 - 1.42), IRE$_{mean}$ (0.008 - 0.006). The maximum variations (mean±st. dev) in these measures from baseline were: $N_{total}$ (311.5±610.5 at week 52), $N_{persistent}$ (24.2±53.7 at week 52), $N_{plateau}$ (237.2±476.8 at week 4), $N_{washout}$ (103.1±192.2 at week 52), $N_{plw}$ (287.2±567.2 at week 52), ME$_{mean}$ (-0.06±0.1 at week 12), IRE$_{mean}$ (-0.002±0.007 at week 4).
Parameters with ‘rough ROI’, placed to exclude muscle tissue and blood vessels, were stable (table 23). The parameters over the year (baseline, week 4, 12, 24, 52) were as follows: \(\text{ME}_{\text{mean}}\) (1.43±0.2, 1.41±0.1, 1.43±0.2, 1.45±0.2 and 1.44±0.2), \(\text{IRE}_{\text{mean}}\) (0.004±0.003, 0.003±0.002, 0.005±0.005, 0.005±0.005 and 0.004±0.004). The maximum variation in these measures from baseline were: \(\text{ME}_{\text{mean}}\) (0.05±0.1 at week 52), \(\text{IRE}_{\text{mean}}\) (-0.001±0.001 at week 4), Normalised persistent (0.46±1.13 at week 12), Normalised plateau (3.56±7.54 at week 52) and Normalised wash-out (1.94±5.9 at week 52).
<table>
<thead>
<tr>
<th>Rough Wrist ROI</th>
<th>Baseline</th>
<th>Week 4</th>
<th>Week 12</th>
<th>Week 24</th>
<th>Week 52</th>
</tr>
</thead>
<tbody>
<tr>
<td>ME_mean</td>
<td>1.43 ± 0.2</td>
<td>1.41 ± 0.1</td>
<td>1.43 ± 0.2</td>
<td>1.45 ± 0.2</td>
<td>1.44 ± 0.2</td>
</tr>
<tr>
<td>ME_std. dev.</td>
<td>0.26 ± 0.1</td>
<td>0.24 ± 0.1</td>
<td>0.26 ± 0.1</td>
<td>0.27 ± 0.1</td>
<td>0.27 ± 0.1</td>
</tr>
<tr>
<td>IRE_mean</td>
<td>0.004 ± 0.003</td>
<td>0.003 ± 0.002</td>
<td>0.005 ± 0.005</td>
<td>0.005 ± 0.005</td>
<td>0.004 ± 0.004</td>
</tr>
<tr>
<td>IRE_std. dev.</td>
<td>0.006 ± 0.005</td>
<td>0.003 ± 0.003</td>
<td>0.005 ± 0.006</td>
<td>0.007 ± 0.007</td>
<td>0.004 ± 0.004</td>
</tr>
<tr>
<td>Normalised Persistent</td>
<td>0.46 ± 0.3</td>
<td>0.76 ± 0.8</td>
<td>0.96 ± 1.2</td>
<td>0.36 ± 0.2</td>
<td>0.96 ± 0.5</td>
</tr>
<tr>
<td>Normalised Plateau</td>
<td>23.61 ± 19.7</td>
<td>26.29 ± 17.9</td>
<td>25.9 ± 22.5</td>
<td>22.46 ± 17.9</td>
<td>24.91 ± 17.6</td>
</tr>
<tr>
<td>Normalised Wash-out</td>
<td>5.5 ± 8.2</td>
<td>5.48 ± 5.1</td>
<td>6.67 ± 6.7</td>
<td>4.38 ± 6.8</td>
<td>7.52 ± 7.1</td>
</tr>
</tbody>
</table>

Mean (µ) and standard deviation (σ)

Table 23: Quantitative parameters for the rheumatoid ‘rough’ ROI over the year

Placement of a precise ROI also demonstrated stable results (table 24). The quantitative parameters over the year (baseline, week 4, 12, 24, 52) were: ME_mean (1.48±0.2, 1.45±0.2, 1.48±0.2, 1.46±0.2 and 1.42±0.1), IRE_mean (0.004±0.003, 0.004±0.003, 0.005±0.005, 0.004±0.005 and 0.004±0.004). The maximum variations in these measures (mean±std.dev) from baseline were: ME_mean (-0.02±0.1 at week 4), IRE_mean (-0.0007±0.001 at week 4), Normalised persistent (0.72±1.6 at week 12), Normalised plateau (6.1±20.2 at week 4) and Normalised wash-out (-3.4±7.9 at week 24).
### Table 24: Quantitative parameters for the rheumatoid ‘Precise’ ROI over the year

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 4</th>
<th>Week 12</th>
<th>Week 24</th>
<th>Week 52</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precise Wrist ROI</td>
<td>( \mu )</td>
<td>( \sigma )</td>
<td>( \mu )</td>
<td>( \sigma )</td>
<td>( \mu )</td>
</tr>
<tr>
<td>( \text{ME}_{\text{mean}} )</td>
<td>1.48</td>
<td>0.2</td>
<td>1.45</td>
<td>0.2</td>
<td>1.48</td>
</tr>
<tr>
<td>( \text{ME}_{\text{st. dev.}} )</td>
<td>0.25</td>
<td>0.1</td>
<td>0.25</td>
<td>0.1</td>
<td>0.28</td>
</tr>
<tr>
<td>( \text{IRE}_{\text{mean}} )</td>
<td>0.004</td>
<td>0.003</td>
<td>0.004</td>
<td>0.003</td>
<td>0.005</td>
</tr>
<tr>
<td>( \text{IRE}_{\text{st. dev.}} )</td>
<td>0.004</td>
<td>0.004</td>
<td>0.003</td>
<td>0.003</td>
<td>0.005</td>
</tr>
<tr>
<td>Normalised Persistent</td>
<td>0.7</td>
<td>0.6</td>
<td>0.72</td>
<td>0.7</td>
<td>1.47</td>
</tr>
<tr>
<td>Normalised Plateau</td>
<td>39.12</td>
<td>23.4</td>
<td>45.23</td>
<td>21.5</td>
<td>40.9</td>
</tr>
<tr>
<td>Normalised Wash-out</td>
<td>9.8</td>
<td>12.4</td>
<td>7.28</td>
<td>5.7</td>
<td>8.51</td>
</tr>
</tbody>
</table>

Mean (\( \mu \)) and standard deviation (\( \sigma \))

6.3.2.4 Correlations between RA patient baseline Synovitis score and DCE-MRI parameters:

The following correlations were seen with synovitis scores-
In whole wrist analysis with $N_{\text{total}} \rho=0.777^* (P=0.008)$, $N_{\text{plateau}} \rho=0.82^* (P=0.004)$, $N_{\text{washout}} \rho=0.722 (P=0.018)$, $N_{\text{plateau}}+N_{\text{washout}} \rho=0.82^* (P=0.004)$, $\text{ME}_{\text{max}} \rho=0.679 (P=0.031)$, $\text{IRE}_{\text{mean}} \rho=0.665 (P=0.036)$.

In ‘rough’ wrist ROI analysis, with $\text{ME}_{\text{mean}} \rho=0.728 (P=0.017)$, $\text{ME}_{\text{st.dev}} \rho=0.661 (P=0.038)$, $\text{IRE}_{\text{mean}} \rho=0.794^* (P=0.006)$, $\text{IRE}_{\text{st.dev}} \rho=0.727 (P=0.017)$, normalised plateau $\rho=0.722 (P=0.018)$.

In ‘precise’ ROI analysis, with $\text{ME}_{\text{mean}} \rho=0.685 (P=0.029)$, $\text{ME}_{\text{st.dev}} \rho=0.661 (P=0.038)$, $\text{IRE}_{\text{mean}} \rho=0.788^* (P=0.007)$, $\text{IRE}_{\text{st.dev}} \rho=0.871^* (P=0.001)$.

### 6.3.2.5 Comparing Maximum enhancement for Healthy and RA:

There was difference in ME between RA and HV subjects in all three methods but more noticeable difference was seen in rough and precise ROI methods (table 25). $\text{ME}_{\text{mean}} > 1.4$ was seen in RA patients for both methods and $\text{ME}_{\text{mean}} < 1.33$ was seen in Healthy subjects.
<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 4</th>
<th>Week 12</th>
<th>Week 24</th>
<th>Week 52</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Whole wrist</strong></td>
<td>µ</td>
<td>µ</td>
<td>µ</td>
<td>µ</td>
<td>µ</td>
</tr>
<tr>
<td>RA $\text{ME}_{\text{mean}}$</td>
<td>1.43</td>
<td>1.38</td>
<td>1.37</td>
<td>1.41</td>
<td>1.42</td>
</tr>
<tr>
<td>HV $\text{ME}_{\text{mean}}$</td>
<td>1.38</td>
<td>-</td>
<td>1.32</td>
<td>1.3</td>
<td>1.34</td>
</tr>
<tr>
<td><strong>Rough Wrist ROI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA $\text{ME}_{\text{mean}}$</td>
<td>1.43</td>
<td>1.41</td>
<td>1.43</td>
<td>1.45</td>
<td>1.44</td>
</tr>
<tr>
<td>HV $\text{ME}_{\text{mean}}$</td>
<td>1.26</td>
<td>-</td>
<td>1.25</td>
<td>1.27</td>
<td>1.29</td>
</tr>
<tr>
<td><strong>Precise Wrist ROI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA $\text{ME}_{\text{mean}}$</td>
<td>1.48</td>
<td>1.45</td>
<td>1.48</td>
<td>1.46</td>
<td>1.42</td>
</tr>
<tr>
<td>HV $\text{ME}_{\text{mean}}$</td>
<td>1.28</td>
<td>1.26</td>
<td>1.32</td>
<td>1.32</td>
<td></td>
</tr>
</tbody>
</table>

*Table 25: Summarises the $\text{ME}_{\text{mean}}$ values for RA and HV for whole wrist, rough wrist and precise ROI techniques*

There was a clear difference between ME values for healthy and RA patients. Figure 40 (A-C) shows box plot graphs with the difference in median ME values for the three methods. When subdividing patients based on moderate disease (DAS >3.2) and comparing with healthy subjects, significant difference was seen at week 24 and 52, for whole wrist $p=0.029$ and $p=0.016$ respectively.
The difference in median ME values for the three methods (A – whole wrist, B – Rough Wrist ROI, C – Precise Wrist ROI).

6.3.2.6 Pattern of enhancement in active RA:

There was a clear difference in the visual pattern of DCE-MRI parametric maps seen amongst patients with DAS ≥ 3.2 (table 26). On subdividing them into less and more active based on visual synovial enhancement, we see that patients with more synovial enhancement have higher ME value, ESR, MRI scores and lesser duration of disease. The
patients with more synovial enhancement had ME: 1.62-1.72 compared to ones with low enhancement ME: 1.17-1.33 (table 27). This would raise the possibility that DAS 28 is not a favourable measure for including patients into studies and an additional imaging synovial measure should be added. It would also be of value to include subjects with early disease and higher inflammatory response, i.e. ESR.

| Patient RA8 | ME \text{mean} & 1.62 & ESR & 44 \text{ mm/hr} & DAS & 5.8 & MRI synovitis score & 6.5 & MRI erosion score & 12 & MRI BME score & 1.5 & Disease duration & 96 |
|-------------|---------------|-------|--------|----------------|----------|----------------|-------|----------------|--------|----------------|--------|----------------|--------|
| Patient RA9 | ME \text{mean} & 1.62 & ESR & 16 \text{ mm/hr} & DAS & 3.95 & MRI synovitis score & 7.5 & MRI erosion score & 21.5 & MRI BME score & 17.5 & Disease duration & 19 |
| Patient RA12 | ME \text{mean} & 1.72 & ESR & 65 \text{ mm/hr} & DAS & 4.49 & MRI synovitis score & 7.5 & MRI erosion score & 14.5 & MRI BME score & 28 & Disease duration & 5 |
| Patient RA13 | ME \text{mean} & 1.67 & ESR & 24 \text{ mm/hr} & DAS & 5.13 & MRI synovitis score & 8 & MRI erosion score & 42 & MRI BME score & 12 & Disease duration & na |
| Patient RA3 | ME \text{mean} & 1.17 & ESR & 14 \text{ mm/hr} & DAS & 3.4 & MRI synovitis score & 5 & MRI erosion score & 3 & MRI BME score & 0 & Disease duration & 120 |
| Patient RA4 | ME \text{mean} & 1.32 & ESR & 11 \text{ mm/hr} & DAS & 4.51 & MRI synovitis score & 6.5 & MRI erosion score & 0 & MRI BME score & 0 & Disease duration & 104 |
| Patient RA5 | ME \text{mean} & 1.32 & ESR & 11 \text{ mm/hr} & DAS & 4.51 & MRI synovitis score & 6.5 & MRI erosion score & 0 & MRI BME score & 0 & Disease duration & 104 |
| Patient RA10 | ME \text{mean} & 1.17 & ESR & 14 \text{ mm/hr} & DAS & 3.4 & MRI synovitis score & 5 & MRI erosion score & 3 & MRI BME score & 0 & Disease duration & 120 |
Table 26: Pictorial tabulation of study parameters and ME parametric map for patients with baseline DAS 28 ≥ 3.2

<table>
<thead>
<tr>
<th>Subject</th>
<th>ESR (mm/hr)</th>
<th>ME\text{mean} (Wrist ROI)</th>
<th>DAS 28</th>
<th>Total Synovitis Score</th>
<th>Total Erosion Score</th>
<th>Total BME Score</th>
<th>RA duration (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visually Less active</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA3</td>
<td>14</td>
<td>1.17</td>
<td>3.4</td>
<td>5</td>
<td>3</td>
<td>0</td>
<td>120</td>
</tr>
<tr>
<td>RA4</td>
<td>11</td>
<td>1.32</td>
<td>4.51</td>
<td>6.5</td>
<td>0</td>
<td>0</td>
<td>104</td>
</tr>
<tr>
<td>RA5</td>
<td>8</td>
<td>1.33</td>
<td>3.2</td>
<td>6</td>
<td>108.5*</td>
<td>11.5</td>
<td>108</td>
</tr>
<tr>
<td>RA10</td>
<td>8</td>
<td>1.23</td>
<td>4.9</td>
<td>6</td>
<td>2</td>
<td>1.5</td>
<td>128</td>
</tr>
<tr>
<td>Average</td>
<td>10.3</td>
<td>1.26</td>
<td>4.0</td>
<td>5.8</td>
<td>1.67</td>
<td>3.25</td>
<td>115</td>
</tr>
<tr>
<td>Visually more active</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA8</td>
<td>44</td>
<td>1.62</td>
<td>5.8</td>
<td>6.5</td>
<td>12</td>
<td>1.5</td>
<td>96</td>
</tr>
<tr>
<td>RA9</td>
<td>16</td>
<td>1.62</td>
<td>3.95</td>
<td>7.5</td>
<td>21.5</td>
<td>17.5</td>
<td>19</td>
</tr>
<tr>
<td>RA12</td>
<td>65</td>
<td>1.72</td>
<td>4.49</td>
<td>7.5</td>
<td>14.5</td>
<td>28</td>
<td>5</td>
</tr>
<tr>
<td>RA13</td>
<td>24</td>
<td>1.67</td>
<td>5.13</td>
<td>8</td>
<td>42</td>
<td>12</td>
<td>na</td>
</tr>
<tr>
<td>Average</td>
<td>37.3</td>
<td>1.66</td>
<td>4.85</td>
<td>7.3</td>
<td>22.5</td>
<td>14.75</td>
<td>40</td>
</tr>
</tbody>
</table>

Table 27: Patients with DAS 28 ≥ 3.2 characterised based on visual disease activity on parametric maps
6.4 Discussion:

There has been a constant evolution of new therapeutic agents being proposed in treating rheumatoid arthritis (397). Evaluation of the therapeutic benefits of a drug intervention highly depends on reliability and sensitivity of the quantitative techniques used. It has been shown that synovitis and marrow oedema are disease activity measures that lead to joint damage in the long term (41, 292). Quantitative analysis for DCE-MRI offers assessment of early disease markers such as synovitis, and is thus anticipated to have an impact on outcome measures from early phase clinical trials in inflammatory arthritis.

Before this method can be used to draw reliable conclusions on the effect of disease modifying drugs, it is important to test it in patients and healthy subjects to determine the inherent and ‘normal’ level of enhancement, which can be expected in routine clinic treated patients and healthy controls. This study validates the background change in automated DCE-MRI parameters over a period of one year.

In healthy subjects erosion-like changes and oedema could be observed on MRI data, but as is known from using 1.0T scanners, the RAMRIS scores were low. Previously Ejbjerg et al., have shown that healthy controls have low RAMRIS synovitis, low dynamic MRI early enhancement and erosion like changes in the wrist joint using lower field strength (1.0T) scanner (373). Palosaari et al, in their study also found erosion like changes and mild to moderate synovial enhancement (401). In the healthy subjects, no erosions were consistently scored by either reader throughout the year; thus emphasising that acquisition
of follow-up images is critical to make reliable conclusions. Also as expected no subject had any radiographic erosion.

In the RA cohort an average of moderate disease activity was seen over the year and though the patients were on standard DMARDS there was a small increase in radiographic erosions over the year. Feet showed most amount of progression, as has been previously described (115).

As expected, there were differences noted between healthy volunteers and RA patients regarding all RAMRIS scores. Mild synovitis scores were seen in healthy volunteers, as compared to moderate for patients. The synovitis scores were done on post contrast images acquired after DCE and thus there was some time delay. It is known from previous studies that early enhancement is due to a combination of synovitis and perfusion, with delayed enhancement due to diffusion into extracellular space (373), hence it’s crucial to acquire post contrast images as early as possible and the reader needs to be aware of this limitation and use all available information to score. Quantitative DCE-MRI synovitis analysis could possibly eliminate some of this bias.

The novel ‘bridge’ positioning device, as described previously, was used to image these patients. This limited motion artefacts, also the inbuilt motion-correction algorithm in the DCE-MRI analysis software further stabilised the images. Hence, the images were as similar to each time-point as possible in their positioning; bearing in mind that imaging was being performed on patients with inflammatory arthritis for prolonged time periods.
The variations in $N_{total}$ and $N_{plw}$ from ‘whole wrist’ DCE-MRI analysis were large over the year. This was due to inclusion of various other soft issue structures in addition to synovial lining, such as blood vessels and muscles. But the ME and IRE remained low and stable. It can be assumed that the fully automated ‘whole wrist’ analysis might be used as a tool to measure change over time after treatment in short follow-ups for RA patients with low-moderate grade synovitis, given that the blood vessel and muscle components of the image would not change significantly. This would significantly speed up the assessment of imaging data as well as take out any human bias, because subjective ROI placements are not needed. This observation is of course to be tested. There were differences in ME values, (baseline – week 52) in healthy (1.38 – 1.34) vs rheumatoid (1.43 – 1.42), though both showed stability over the year. Maximum change in ME was low, for patients it was -0.06±0.1 at week 12 and for healthy subjects -0.08±0.1 at week 24. This highlights the stability of this method in longitudinal analysis.

Analysis with the ‘rough’ ROI gave accurate and similar stable results throughout the year as compared to the analysis with the ‘precise’ ROI and required much less time to outline the anatomy of interest. Both techniques saw minimal change in ME_{mean} and IRE_{mean} values over a year in both healthy (407) and rheumatoid patients (408). There could be various reasons for this small variation including intrinsic software instability, normal physiological change in healthy and stable RA patients, body and surrounding temperature, vascular flow kinetics, and degree of activity at the joint. These hypotheses would need testing in future studies. Also similar results were seen in healthy volunteers and RA patients. This generates a possible similarity in perfusion measures in stable study groups and hence the need to recruit active and early subjects in clinical trials.
In the sub-analysis of subjects with DAS 28 >3.2 there were two distinct patterns of enhancement, suggesting that DAS 28 may not be a favourable inclusion measure as compared to quantitative parametric measures like DCE-MRI, and including patients with early arthritis who have a more significant synovial disease burden would be advisable. It was also possible to define cut off points in ME for patients and healthy subjects which will also enable to define thresholds for patients entering clinical trials using DCE-MRI. These cut off points could also be used to define DCE-MRI imaging remission goals in RA patients.

The limitations of this study included subject size, but it nevertheless defines background change/variability in automated quantification of DCE-MRI wrists. These findings are crucial for understanding the level of the various DCE-MRI enhancement parameters in healthy controls and stable rheumatoid patients which is important information when discussing or defining imaging remission criteria in designing future clinical trials.

These results demonstrate that dynamic parameters obtained using fully automated analysis correlate well with RAMRIS scores, and allow for robust and sensitive analysis. The reliability of these measures paves way for utilization of this technique in assessment of therapeutic interventions.
7 Overall Discussion and Conclusion
The work presented in this thesis was aimed at looking at computerised analysis tools for MRI and radiographic RA disease activity measures longitudinally over time, while imaging at short and long time intervals on a high field strength (3 Tesla) MRI. The work has been presented as preliminary and main studies. The preliminary work was about development of a patient positioning device ‘the bridge’ for wrist imaging, which was subsequently used in a yearlong longitudinal study of RA patients. While imaging patients hands and wrist, the bridge positioning device allowed patients, in a supine position, to position their hands over their abdomen with comfort and good quality reproducible image capture. The main study was a longitudinal observational study of RA patients on routine treatment and healthy subjects using 3T wrist MRI, hand and feet radiographs and analysis using exploratory and new computerised methods in pilot sub-studies. Techniques that were assessed included bone segmentation methods both manual and semi-automatic, with a view to speed up analysis, quantify volume change and change in bone shape over time. The registration and transformation technique allowed evaluation of small changes visually. The pilot work using computerised digital X-ray radiogrammetric analysis identified correlations between rate of bone mineral density loss with BME change at 1 year, which is known to be a predictor of future erosions and generated hypothesis that this may represent earlier disease activity measure. The work using computerised DCE-MRI analysis highlighted that the dynamic parameters obtained correlate well with RAMRIS scores, and allow for robust and sensitive analysis. The reliability of these measures paves way for utilization of this technique in assessment of therapeutic interventions.

To acquire good quality wrist images, without motion artefacts, the patient should be in a as comfortable a position as possible (321). For wrist examinations, the currently used patient
positions include: ‘superman/swimmer position’ (prone with hand above the head) (22, 409) and hand by the side of the body while lying supine (146, 272, 302, 322, 323).

The superman/swimmer position places the wrist close to the isocentre but can be difficult to tolerate for patients due to joint pains and result in motion artifacts (324-326, 409, Berquist, 1989 #320). RA patients can also find it difficult to remain in a strenuous position for a long time during examinations (327), with possibility of incomplete studies due to discomfort in upto 25% of patients (325, 328). DCE-MRI sequences used for quantitative synovial enhancement analysis require patients to lie still (329) as small changes / motion can affect quantitative analysis. Thus scanning patients in a more comfortable position can help to reduce some of these limitations with current wrist imaging positions. The hand by the side position provides a comfortable pose, but places the wrist at the very edge of an operation field of view of the scanner and can result in poor signal to noise ratio in images.

The bridge positioning device developed addressed the issues posed by current positions, it allowed for comfortable positioning compared to both superman/swimmer and hand by the side positions and with intermediate image quality. The various 7 measurements taken during patient positioning using the device also enabled reproducible imaging.

There was good patient co-operation for the extended study examinations lasting up to 45-60 minutes and to a large extent the patient positioning device helped to scan them in a position of greater comfort. By using a dedicated wrist coil optimal image quality and targeted examination was possible. Recent studies have shown that dedicated extremity coil and high strength MRI allows for better disease activity measurement (308, 320). Eshed et
al., in their study found that field strength and coil type influence synovitis assessment, and this should be taken into consideration while performing MRI in clinical practice and research trials (320).

The ‘bridge’ device was scored highly by both patients and healthy subjects for comfort in the main longitudinal study. In addition to holding the wrist stably in a comfortable position as close as possible to isocentre, the systematic set of measurements allowed for reproducible positioning. Thus the developed bridge device offers an alternative patient positioning method in wrist MR imaging.

The main study was an exploratory study investigating disease activity in rheumatoid arthritis subject hand joints detected by high field strength wrist magnetic resonance imaging (MRI) and radiographs over a series of short time intervals over a year. The emphasis was on computerised image analysis methods. Initial work was done in evaluating various bone segmentation methods to assess bone shape, change over time both morphological and volumetric. Manual technique to precisely delineate the bones on T1 weighted images has been described previously (342) and was initially used for analysis, but this was time consuming, taking up to 2 hours to segment one carpal bone. In one healthy study subject one wrist MRI took 936 minutes to segment 14 bones (530 image slices). Using manual segmentation there were high inter and intra-observer similarity results for bone segmentation. Manual segmentation approach using similar principals have recently been used to segment erosions in a study investigating reliability, feasibility and validity of this method (303). They showed high intra and interobserver reliability for segmenting erosions
A one dimension erosion semiquantitative measurement has also been used, where a linear maximal erosion dimension in axial plane was performed (346, 410).

The other method using a different software tool, SliceOmatic, based on different signal intensity threshold matrix and fat suppressed images for better bone margin delineation was similarly time consuming 3256 minutes for 2196 image slices for 8 RA patients. Long segmentation time data has been described in published studies for manual method (322, 342). The lack of automation severely limits this method as a potential in regular clinical or large research studies (342), but still has a role in small patient groups where single or target bone is being assessed and followed up. The process of image registration and transformation of future images, based on segmented bone masks, allowed visual analysis of subtle changes. Though the cohort in this study was stable, small visual changes were seen using this method. This technique potentially has a role in better follow up image alignment while using visual assessment or semiquantitative scoring.

The semiautomatic bone segmentation using signal thresholding method was much quicker than manual method and works well in healthy and patients with low disease activity. As the thresholding fails in high disease activity state some degree of manual refinement of the analysis would still be required. This hypothesis though needs testing in larger cohort with varied disease activity status. This method can also be applied to assess other disease measures like BME and synovitis, though this was not evaluated in this work.

In the main study patients were on routine treatment and had stable moderate DAS 28 disease scores (Day 1, Week 4, 12, 24, and 52 mean scores were 3.9, 3.6, 4.0, 3.9, and 4.0
respectively). The MRI semi-quantitative scores showed no significant change over the year, but there was a minimal increase in overall radiographic score largely due to progression in the feet. 60% of the study patients (n = 6) progressed in radiographic scores, albeit with a small rise over a year (0.4%). 1 patient (10%) had change more than MDC_{95}. The majority (66%) of the patients that did progress showed progression in feet, which were largely due to erosions. Periodic evaluation of joint damage by radiographs is one of the European League Against Rheumatism (EULAR) task force recommendation, with MRI and possibly ultrasound used to monitor disease progression (223).

It is known from previous studies that feet erosions progress earlier than hands (223, 411-413). Van der Leeden et al., in their study found that prevalence and severity of forefoot damage increases during the first 8 years of RA (412). They studied 848 patients with recent onset RA and found 70% had pain and swelling in metatarsal phalangeal (MTP) joints at baseline. 19% patients had baseline erosions which increased to 60% at 8 years follow up, with increase in mean erosion scores. Lindqvist et al., in their study of early RA patients (mean duration < 1 year), found 37% of patients had feet erosions compared to 27% in the hands (413). It is also known that foot involvement occurs frequently in early RA when assessed with MRI (224) and forefoot MRI shows synovitis and BME when MCP MRI is normal (411). Olech et al., in their study showed that extremity MRI of both hands and feet identified more erosions than just one or both hand assessment (414). The MRI OMERACT scores wrist and MCP and a modified version for forefoot has been described (411). A modification with an emphasis on dynamic MRI to assess perfusion changes in the joint would also be of value to similar work that has been done in wrist DCE-MRI in this thesis.
There could be many reasons why feet progress earlier compared to hands, including different biomechanics translating across the various joints in the feet, increased perfusion in the soft tissue due to weight bearing joints, micro trauma and an element of degenerative change which can lead of joint space narrowing. Recently, Dubbeldam et al., have shown moderate to strong relationships between foot and ankle gait kinematics and structural abnormality (415).

Indirect evidence of altered biomechanics and mechanical stress could be that bursitis in between and beneath metatarsal heads is more common in patients with early RA (416). These hypotheses though need testing and a regular assessment of feet and hands with more advanced techniques like MRI or ultrasound would be of value. Siddle et al., in their recent study looked at anatomical location of erosion in the feet on 3T MRI. They found that erosions in RA were more commonly seen on the plantar aspect of the metatarsal head, supporting relationship between biomechanical demand and bone change in the feet (417). Plantar plate pathology and associations with RAMRIS synovitis, BME and erosion at the 4th and 5th MTP joints has also been shown (418).

Another recent study, has shown that dominant hand have worse radiological damage and progress faster than non-dominant hand suggesting mechanical stress as contributing factor (299). It is also known that increased radiographic damage scores in older patients are associated with osteoarthritis (419). Mangnus et al., in a study of 1875 RA patients and 7219 radiographs revealed an increase in radiographic joint damage scores per year increase in age (420). This needs to be taken into consideration by the image reader when assessing hand and feet radiographs in RA.
There were correlation between MRI measures in the main study, between BME and MRI erosion and synovitis. Even though no significant disease activity change was seen in these patients on routine clinical care over the year, nevertheless the score correlated with each other showing that synovitis, BME and erosions are all inter-linked in the joint based disease process in RA as has been extensively described (262, 283-285, 360, 395, 421-423). Post treatment improvement in these MRI measures also emphasises this relationship. Rituximab, a monoclonal antibody against protein CD20 in a recent phase 3 study, was used to treat active RA patients. There was significantly less progression in patients mean erosion scores amongst those that were treatment with Rituximab as compared to placebo, with also improvement in synovitis and BME scores (424).

There were very small increases in MRI erosions (1.6%), BME (0.8%) and radiographic scores (0.4%). This could infer that patients with moderate disease despite being on standard clinical care show small progression in erosions both on MRI and radiographs. It is known that radiographic progression can continue even when there is reduction in clinical disease activity (425). This has been attributed to continued inflammation in the joint on advanced imaging which can be subclinical (62, 64, 404). Subclinical MRI joint inflammation can also be seen in early undifferentiated arthralgia patients that progress to RA (404). In this study there was moderate synovitis on MRI semiquantitative assessment with mean scores ranging from 5.8 at Day 1 to 5.1 at week 52 and is likely to have a contributory effect in joint damage.

It is well known that RA patients have periarticular osteopenia (385) and BME leads to erosions (284, 423). DXR has been described to be better than DXA for detecting and
monitoring periarticular osteopenia of the metacarpal bone (176). DXR BMD loss is known to be a predictor of future erosions in RA (181, 188) and has been identified as a surrogate marker for radiological progression in RA (183). DXR measurements have been described to be more precise than radiographic scores (189). As part of the main study DXR analysis, early metacarpal RC-BMD loss at 3 months correlated with wrist BME change at a year, though no correlations were seen with erosions at 1 year.

Inflammation within the bone is seen as osteitis or BME on MRI. In RA, inflammatory cytokines are linked to increased bone loss (199). Similar pathogenic mechanisms leading to hand bone loss and erosion in RA have been proposed (200). BME is the most specific finding seen on non-contrast MRI in RA patients (372). BME also has similar signal characteristics to inflamed synovium (426), with bone lesions near the joint showing increased vascularity, perfusion and high water content (426). The relationship between serum inflammatory cytokines and BME was also recently evaluated by Li et al (427). They assessed the relationship between BME and serum receptor activator of nuclear factor kappa-B ligand (RANKL), serum osteoprotegerin (OPG) amongst others and found correlations with severity of BME (427).

In RA, synovium has been well regarded as major site of disease process. Although the pathogenesis and clinical importance of synovitis is beyond question, more recently it is becoming increasing clear that just ‘synovio-centric’ model of RA may be limiting (421, 428). Subchondral bone has also been shown to be involved in the disease process (287, 426, 428-431). Dysregulated B cell response and autoreactivity in part occurs in the bone marrow (432). Schett et al., postulated an ‘outside-in’ and ‘inside-out’ concept of joint based
inflammation in RA (433). The outside-in concept is where the inflammation starts in the synovium and later spreads into the adjacent structures and bone marrow. Alternatively the inside-out concept is where the process starts in the marrow and encroaches into the synovium (433).

Immunohistochemical characteristics of subchondral bone marrow in RA patients undergoing joint surgery have also shown increased osteoclasts and lymphoid aggregates in the subchondral bone. Local inflammation/aggregation related to osteoclast differentiation support role of bone based local damage (434). Jimenez-Boj et al., investigated pathologic nature of MRI erosion and BME in RA joints. They assessed joints with MRI prior to joint replacement surgery. Fat rich bone marrow was found to be replaced with inflammatory tissue, increased water content and was bright on fat suppressed images. MRI BME was shown to find inflammatory infiltrates and found in contact with MRI erosions (284). MRI BME has also been shown in the surgical field of joints of RA patients undergoing joint replacement (423) with osteitis on histology (423). Infiltration of macrophages, plasma cells, T cells, B cell aggregates, increased osteoclasts was seen in the area of BME on preoperative MRI in a study by Dalbeth et al (435).

Extensive BME has been described in patients with undifferentiated arthritis who later develop RA (288). BME is also known to predict future radiographic joint damage in RA (198, 292, 396).

DXR BMD loss is commonly seen in RA and is known to be a predictor of future development of RA in recent onset arthritis (386), and also future damage (186, 190, 391). Increased bone
loss as measured DXR also correlates with increased serum inflammatory markers like MMP-3 (436). Inflammatory cytokines such as TNF and IL6 have been linked with increased osteoclastic activity, which have been associated with alteration of bone metabolism in early RA (392, 393). Therapies inhibiting inflammatory cytokines have shown to reduce bone loss in RA (203). It has been recently described that Infliximab, an anti-TNF, agent improves bone mineral density and metabolism in rheumatoid arthritis (394). Higher 3 month DXR BMD loss has been described in patients with MRI erosive disease (198). Given that subchondral BME and periarticular osteopenia can seen in a similar locations, have inflammatory cytokine relationships, and lead to future damage, there could be a relationship between these measures.

In the main study, as part of the pilot work using DXR analysis and high field strength MRI, early metacarpal RC-BMD loss at 3 months correlated with wrist BME change at a year, though no correlations were seen with erosions at 1 year. Some of the reasons for this could be that the patients were mostly with established RA on standard combination of disease modifying therapy. Studies have looked at early RA or undifferentiated arthritis and these cohorts were often selected for poor prognostic factors and thus exhibited a much faster average rate of structural damage. Also a hypothesis could be that in patients with established RA on standard clinical care these findings could reflect a slower kinetic in the appearance of MRI/radiographic erosion than that of RC-BMD change thus generating the hypothesis that RC-BMD may be a sensitive and early structural prognostic marker in RA follow-up. Though, further studies assessing DXR BMD loss and MRI features of osteitis are required to understand the disease associations further, both with and without therapeutic interventions. This study findings, though from a small cohort of patients, has potential for
future exploration in larger studies of patients with early RA. These patients are not likely to have a large burden of erosions which thereby makes assessments easier.

In the DCE-MRI analysis part of this work, the low variability/background change of DCE-MRI parameters in both healthy volunteers and RA patients has positive value in showing stability of the software over a year in subjects who do not have significant change over the year. This is crucial when these methods are to be used in evaluating changes due to new treatment interventions in the future. Prior to RAMRIS scores, manual segmentation of the synovium was used to assess treatment response but this method was time consuming (352, 365, 437). Semi-automating synovial volume measurement are known to reduce reading time from 45 - 120 minutes to 5 - 20 minutes (277). Automating methods helps to speed up the analysis process. Boesen et al., compared manual and computer aided techniques for evaluating wrist synovitis using DCE-MRI (350), and found that the computer-aided method generated robust and reproducible results (350). DCE-MRI provide fast and accurate assessment of synovium (361) and parameters such as IRE have shown to correlate with histological inflammation (361).

Studies have used single or few DCE MRI slices for analysis (329, 350, 351, 362, 363). In this study, large amount of 3D data set was analysed at each time point for every patient (127 slices with 40 frames = 5080 temporal frames). This also enabled testing of software stability further, as it was able to analyse large data volumes and extract results for each slice as part of the whole wrist analysis. The analysis was quick, with most time taken in uploading, image data processing and motion correction. The user analysis was relatively quick; up to 15 minutes per MRI scan.
There was a difference in mean maximum enhancement (\(\text{ME}_{\text{mean}}\)) seen in patients and healthy subjects and there were also differences in the visual analysis maps. These results were also mirrored in the RAMRIS scores. The differences in \(\text{ME}_{\text{mean}}\) values were more pronounced in rough and precise ROI assessments. \(\text{ME}_{\text{mean}} > 1.4\) was seen in RA patients for both methods and \(\text{ME}_{\text{mean}} < 1.33\) was seen in Healthy subjects. This indicated that in patients > 40% increase can be seen in ME from baseline after contrast injection, and in healthy subjects the enhancement is < 33% from baseline. Recently, Axelsen et al, using 1T MRI and single slice DCE-MRI, showed that enhancement occurred in healthy subjects (438). In this study too synovial enhancement was seen in healthy subjects and to a large extent this was due to contrast in the extracellular space, which can occur with delayed imaging and is difficult to differentiate from synovium (373).

Dynamic parameters correlated with RAMRIS synovitis scores in healthy subjects and RA patients. Similar findings have been seen recently with low field strength 0.2 T MRI (363, 369). Lee et al., recently compared DCE-MRI on low field (0.25T) with high field (3T) and found that low field correlated well with high field strength with regards to RAMRIS score and synovial volume measurements with fair to good correlations for perfusion parameters (231). Though the low field MRI can be limited in its evaluation of BME (439), with considerable intermachine and inter-reader variability (440). Navalho et al., in their study supported the use of 3T DCE-MRI for precise quantification of disease activity and for discriminating active and inactive early polyarthritis (441).

Inflammation on MRI is not only present in clinically swollen but also in non-swollen joints. Subclinical inflammation has been identified by MRI in the majority of RA patients in clinical
remission or low disease activity state. This may explain structural progression in such patients. Further work is required to understand the place of modern imaging in future remission criteria (64). The relevance of subclinical inflammation for the disease course is a subject for further studies (442) and DCE-MRI analysis has a role in this. The analysis in this thesis can act as a measure of minimum change that is seen in healthy subjects and stable RA subjects and thus act as cut off thresholds in clinical trials using this technique.

DCE-MRI also has a role in assessing enhancement characteristics of synovitis pre and post therapeutic intervention. In a study using anti-TNF and 3T MRI of interphalangeal joints it was seen that signal intensity time curves changed significantly post treatment and the authors concluded that this method holds promise for monitoring therapy (443). Further research needs to be done using this method to assess therapeutic intervention in other joints including wrist, MCP and MTP joints which are commonly involved in RA. In a recent study with a similar approach, Cimmino et al., studied the prospective effect of rituximab on 10 RA patients using a 0.2T MRI system, and performed pre and post contrast imaging in addition to DCE-MRI. They found the RAMRIS scores did not change over time (0, 4 and 24 weeks) but there was significant decrease in perfusion measures including ME and IRE over the same period (444). Axelsen et al., in their study used DCE-MRI in their study using methotrexate, intra-articular triamcinolone with or without adalimumab and showed the DCE-MRI parameters including ME and IRE correlated with RAMRIS (445).

There was good patient compliance for our extended examinations and to a large extent the patient positioning device helped to scan them in a position of greater comfort. By using a dedicated wrist coil and targeted examination optimal image quality was possible. The
‘bridge’ device also allowed for positioning with minimal motion artefact. This along with
the motion correction inbuilt in the DCE-MRI analysis software (329) helped in the analysis
by enabling the results were related to disease activity and not altered by motion artefact.
The achievements from the study have been summarised further in the next section.

7.1 Achievements:

This work evaluates high field strength 3T MRI, digital radiographs and computerised
analysis tools. The following are the summarised achievements:

- The preliminary study successfully developed, tested and implemented a patient
  positioning device in wrist imaging, which was subsequently used in the main study.
- Evaluation of bone segmentation was performed using both manual and semi-
  automated techniques with comparative analysis in a pilot work. The segmentation,
  registration and transformations techniques can be used to follow-up future time
  points and assess small changes.
- In the main study radiographs were assessed with computerised digital X-ray
  radiogrammetric technique which found that early metacarpal rate of change in
  bone mineral density loss correlates with wrist bone marrow oedema change at 1
  year, which is a known marker for future erosions.
- In the DCE-MRI analysis part of this work, the low variability of DCE-MRI parameters
  in both healthy volunteers and RA patients has positive value in showing stability of
  the software over a year in subjects who do not have significant change over the
  year. The DCE-MRI parameters correlated with semi-quantitative synovitis scores.
• The study demonstrated successful academic-industry collaboration (section 2.2.4.3) which resulted in joint work in translating concepts, study design, implementation, analysis and effects which aim to help in direct patient care. Industry Collaborations were with IXICO Ltd, UK; SECTRA, Sweden; and Image Analysis, UK. Funding was provided by GlaxoSmithKline, UK.

7.2 Study limitations and challenges:

There were several challenges that were faced during the course of the study and analysis:

• The main study start was delayed by various factors including new developments regarding Gadolinium contrast exposure and its association with nephrogenic systemic fibrosis (446-451). This required work on the protocol, a literature review, approval from the safety department of the sponsor and substantial amendment to the ethics application. The association between Gd exposure and nephrogenic systemic fibrosis is now well known and described (452-456).

• Recruitment was slow into the study in spite of extensive recruitment talks to referring clinicians. Interval ethics approval was obtained for various forms of recruitment adverts. The study inclusion criteria were rigid, which required patients to have both positive serology and radiographic erosions. During the initial drive, the author found that many patients who were keen and with early active RA, did not have erosions on radiographs. It has been previously described that radiographic erosions lag behind MRI (49, 215). Hence this criterion was relaxed, and amended for erosions to only be necessary if serology was negative.
The other challenges to recruitment included patient claustrophobia, the need for multiple visits and thus patient time constraints. To accommodate the latter, reimbursement for patients’ time was also included. Subsequent to the change in inclusion criteria, we experienced a small increase in recruitment. In June 2008 the study sponsor decided not to continue to support the study based on the difficulty in subject recruitment to enable the objectives to be met and any further recruitment was stopped but allowed subjects in the study to continue. The academic interest in the study centred around the exploratory analysis and new image analysis techniques; and it was decided that Imperial would act as the study sponsor and see that these subjects complete all study visits. This required substantial ethics amendments.

A major limitation of this study lies in its small number size. Although there were a limited number of volunteers and thus limited longitudinal data, the presented data still helps to draw various conclusions of significant value and importance both in a clinical and research setting. The study gives us the opportunity to explore new imaging potential biomarkers both on radiographs and with new MRI techniques. Assessments with even small patient and healthy subject numbers are important as normal data is extremely valuable in the future assessment of inflammatory arthritis. The pilot work using bone segmentation, DXR, and DCE-MRI generate hypothesis for future studies that will need to be tested in larger cohort, defined patient groups and different MRI imaging platforms. Nevertheless, this is, to the author’s knowledge, the only study to evaluate RC-BMD using DXR and 3T wrist MRI in a longitudinal fashion in established RA patients with wide range of disease duration. In the DCE-
MRI analysis part of this work, the low variability of DCE-MRI parameters in both healthy volunteers and RA patients has positive value in showing stability of the software over a year in subjects who do not have significant change over the year. This is crucial when these methods are to be used in evaluating changes due to new treatment interventions in the future.

- A limitation with the DXR analysis is that this method requires two images to be acquired 3 months apart and with the same type of X-ray modality. The system automatically rejects change calculations when the same modality type is not used. If all the same types of X-ray modalities were upgraded simultaneously, BMD change during the upgrade period will not be possible.

- A possible limitation of the bridge comfort assessment during the main study was that a comparative assessment with the other two positions was not done on RA patients, as was performed on healthy subjects in the preliminary study. This would have been helpful as the ‘hand by the side’ position is more commonly used in practice.

### 7.3 Future direction:

The results presented in this work potentially lead to many future research ideas. The possible combination of forging a way of combining manual with semi-automatic techniques would be a way forward in bone volume segmentation and follow-up. This requires further work on how to address the challenge in patients with extensive erosive disease. In the pilot work, the semi-automated method centred on signal thresholding failed in eroded bones, but worked well in bones with low or moderate disease. Thus this method has potential in
early disease where the number of erosions would be lower and easier to use semi-automated techniques.

The ability to precisely assess each bone, using registration and transformation techniques, allows follow-up of small changes visually. This could be integrated into PACS with possible potential benefit in regular clinical assessments. This method is also of value in early disease where small changes would require follow-up and early intervention.

In this work, BME segmentation was not performed, and the manual and semi-automated segmentation method using signal thresholding techniques could be applied in future studies for BME and synovitis. Recently, a few studies have looked at the feasibility and reliability of this technique (346, 457), but work still needs to be done to assess its responsiveness to treatment strategies. Kamishima et al., have also used signal thresholding method to assess synovitis quantification (458) but have stressed importance of identifying correct thresholds for accurate analysis.

The findings from DXR analysis needs to be assessed in large studies using MRI with routine digital radiographs. This modality offers potential in that it can be explored further as a technique to follow-up patients in a clinical setting. This is possible in current practice as digital radiographs are now the standard given the digital radiology workflow. Large epidemiological studies could thereby be designed by using this resource on a regional or national level. Further studies assessing DXR BMD loss and MRI features of osteitis would be helpful to understand the disease associations further both with and without therapeutic interventions.
Having quantified DCE-MRI parameters in healthy and stable RA patients, this method needs to be tested with drug intervention. There have been studies which have explored this in the setting of steroid injection into the joint (371, 459), and biologic therapies (444, 445, 460). The degree of change needs to be quantified with regards to currently used therapeutic medications including DMARDS, steroids and biologic therapies. Once this is quantified it paves the way to use this method in new molecule studies, as baseline and degree of change would have been set as references for interventions to be assessed against. The results from this work also help to define targets for remission goals using this method.

The value of DCE-MRI in multicentre clinical trials, e.g. reproducibility between different scanners, sensitivity to treatment change, and predictability to future joint progression needs exploration. The technique also needs to be explored in other joints, like forefoot which is commonly involved in RA and are known to progress quicker in early disease. A recent study has looked at DCE-MRI and tissue segmentation which can be further explored (461).

Other non-invasive MRI methods that can be used in synovitis assessment include - arterial spine labelling (ASL), diffusion weighted imaging (DWI), diffusion tensor imaging (DTI) and fluorine-19 MRI. ASL, DWI and DTI sequences are routinely used in neuroimaging and offer translational potential in rheumatic disease. Boss et al., used ASL perfusion imaging in inflammatory arthritis and found it to be of potential in assessing joint inflammation and does not require contrast administration (462). In a feasibility study of DWI for assessing RA
wrist synovitis, Li et al., found that DWI showed inflammed areas better than T2 weighted image, and it presents an non-invasive contrast free technique in imaging synovitis (463). There are no other known published works using this method in RA wrist imaging and further studies are required to evaluate DWI with DCE-MRI, and standard semi-quantitative RAMRIS scores. Future work should also look at its role in quantitative analysis, its validity, reliability and responsiveness in RA therapeutic intervention.

A pilot study using DTI to assess synovial inflammation was performed by Agarwal et al., and suggested that the DTI derived results have the potential to delineate synovial inflammation but is not superior to conventional MRI for detecting and assessing therapeutic response (464). Balducci et al., in their study showed perfluorocarbon contrast which labels inflammatory cells enabled detection of inflammation by 19F-MRI in their study of collagen-induced rat arthritis as a model (465). These new computerised methods and sequences thus offer great potential in future research work.

### 7.4 Conclusion:

A ‘bridge’ device for patient positioning was developed which allowed good repositioning. Subject comfort was higher than, and image quality was intermediate between, the reference standard positions tested, indicating that the device was fit for purpose. This was successfully implemented in a longitudinal yearlong study.
In the bone segmentation work, the semi-automated method was much quicker than manual, but failed in advanced RA patient. A combined approach points the way forward in this area. Registration and transformation work of follow up bone analysis also allowed visual detection of small changes in disease activity over time.

The longitudinal main study showed no significant change in disease activity over time, though correlations were seen between various MRI disease activity measures. Bone marrow oedema correlated with erosion at week 24 and 52 on MRI and automated metacarpal RC-BMD loss over 3 months correlated with wrist BME change at 1 year. BME is a known predictor of erosions. However, in this cohort there was no correlation between RC-BMD and erosions. This raises the possibility that in patients with established RA on standard treatment and a low annualized rate of radiographic progression, DXR may offer a tool as an early indicator of insidious damage progression over the longer term. These findings and the generated hypothesis need to be further evaluated in larger cohort of patients.

The DCE-MRI work also demonstrated that contrast enhancement does occur in healthy volunteers but the perfusion measures obtained with quantitative method remain stable, suggesting its suitability for longitudinal studies of inflammatory arthritis. Similar stable perfusion measures were seen in rheumatoid patients over a year. These results potentially provide important information regarding imaging remission and therapeutic intervention target goals in patients with RA using DCE-MRI.
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9 Publications and presentations as a result of this work

The following is the list of publication and presentations from this study.


• **Anshul Rastogi**, Olga Kubassova, Lada V. Krasnosselskaia, Adrian K.P. Lim, Keshthra Satchithananda, Mikael Boesen, Michael Binks, Joseph V. Hajnal, Peter C. Taylor.

  Evaluating automated dynamic contrast enhanced wrist 3T MRI in healthy volunteers: One-year longitudinal observational study.


Correlating Digital Bone Mineral Densitometry (DXR-BMD) and 3T wrist MRI change over a year in Rheumatoid Arthritic (RA) joints (A003) (Abstract). Skeletal Radiology (2012) 41:871.

European Society of Skeletal Radiology meeting, Innsbruck, Austria. 29th June 2012 - Oral Presentation.

• **Anshul Rastogi**, Olga Kubassova, Mikael Boesen, Joseph V. Hajnal, Peter C. Taylor.


American Congress of Rheumatology, 7th Nov. 2011, Chicago, US – Poster.


Semi-automating bone segmentation from MRI wrist images: Application in clinical trials in rheumatoid arthritis (RA).


European Congress of Radiology, Vienna 6-10th March 2009 – Scientific Exhibit.

Also presented at MRS / AMS / RCP Clinical Scientists in Training meeting, Royal College of Physicians, London, 26th Feb. 2009 – Poster

• **Anshul Rastogi**, Lada V. Krasnosselskaia, Emer J. Hughes, Nadeem Saeed, Jane S. Angwin, Michael H. Binks, Peter C. Taylor, Joseph V. Hajnal.
Evaluating a novel positioning device in Magnetic Resonance Imaging (MRI) of the Wrist.

ISMRM workshop in advances in musculoskeletal MRI, San Francisco, 16th February 2009 – Oral.


- **Anshul Rastogi;** Lada V. Krasnosselskaia; Emer Hughes, Giuliana Durighel, Nadeem Saeed; Jane S. Angwin; Michael H. Binks; Neeteesha Newell; Peter C. Taylor; Joseph V. Hajnal.


- Lada V. Krasnosselskaia; **Anshul Rastogi;** Nadeem Saeed; Jane S. Angwin; Michael H. Binks; Neeteesha X. Newell; Peter C. Taylor; Jo V. Hajnal.

  Getting past the pain barrier towards successful wrist imaging.

  British Chapter of ISMRM, Birmingham. 6th Sept. 2007 – Poster (P7).
Evaluating automated dynamic contrast enhanced wrist 3 T MRI in healthy volunteers: One-year longitudinal observational study

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ABSTRACT

Rationale and Objective: Dynamic contrast enhanced (DCE)-MRI has great potential to provide quantitative measure of inflammatory activity in rheumatoid arthritis. There is no current benchmark to establish the stability of signal in the joints of healthy subjects when imaged with DCE-MRI longitudinally, which is crucial so as to differentiate changes induced by treatment from the inherent variability of perfusion measures. The objective of this study was to test a pixel-by-pixel parametric map based approach for analysis of DCE-MRI (DYNAMICA) and to investigate the variability in signal characteristics over time in healthy controls using longitudinally acquired images.

Materials and Methods: 10 healthy volunteers enrolled, dominant wrists were imaged with contrast enhanced 3T MRI at baseline, week 12, 24 and 52 and scored with RAMRIS. DCE-MRI was analysed using a novel quantification parametric map based approach. Radiographs were obtained at baseline and week 52 and scored using modified Sharp van der Heijde method. RAMRIS scores and dynamic MRI measures were correlated.

Results: No erosions were seen on radiographs, whereas MRI showed erosion-like changes, low grade bone marrow oedema and low-moderate synovial enhancement. The DCE-MRI parameters were stable (baseline scores, variability) (mean ± std), in whole wrist analysis, MRTank (1.3 ± 0.7, 1.00 ± 0.1 at week 24) and IRTtanked (0.001 ± 0.004, 0.002 ± 0.005 at week 12 and 24). In the nongraft ROI, MRTank (1.2 ± 0.07, 0.04 ± 0.02 at week 52) and IRTtanked (0.001 ± 0.0008, 0.0005 ± 0.0009 at week 52) and precise wrist ROI, MRTank (1.2 ± 0.09, 0.04 ± 0.04 at week 52) and IRTtanked (0.001 ± 0.0008, 0.0008 ± 0.001 at week 24 and 52). The dynamic parameters obtained using fully automated analysis demonstrated strong, statistically significant correlations with RAMRIS synovitis scores.

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Research Article

Early Metacarpal Bone Mineral Density Loss Using Digital X-Ray Radiogrammetry and 3-Tesla Wrist MRI in Established Rheumatoid Arthritis: A Longitudinal One-Year Observational Study

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Objectives. Early change in rheumatoid arthritis (RA) is characterised by peripheral osteopenia. We investigated the relationship of early metacarpal digital X-ray radiogrammetry bone mineral density (DXR-BMD) change rate (RC-BMD, mg/cm²/month) and longitudinal changes in hand and feet radiographic and wrist MRI scores over 1 year. Materials and Methods. 10 RA patients completed the study and had wrist 3T-MRI and hand and feet X-rays at various time points over 1 year. MRI was scored by RAMRIS, X-ray was done by van der Heijde modified Sharp scoring, and RC-BMD was analysed using dxr-online. Results. There was good correlation amongst the two scorers for MRI measures and ICC for erosions: 0.984, BME: 0.943, and synovitis: 0.667. Strong relationships were observed between RC-BMD at 12 week and 1-year change in wrist marrow oedema (BME) (r = 0.78, P = 0.035) but not with erosion, synovitis, or radiographic scores. Conclusion. Early RC-BMD correlates with 1-year wrist BME change, which is a known predictor of future erosion and joint damage. However, in our pilot study, early RC-BMD did not show relationships to MRI erosion or radiographic changes over 1 year. This may reflect a slower kinetic in the appearance of MRI/radiographic erosions, generating the hypothesis that RC-BMD may be a more sensitive and early structural prognostic marker in RA follow-up.

1. Introduction

Radiographic imaging (X-ray) has traditionally been important in diagnosis, as per 1987 American College of Rheumatology (ACR) criteria [1] and subsequent evaluation of patients with rheumatoid arthritis (RA) [2–4]. Evaluation of the extent and rate of structural damage in routine clinical practice involves hand and feet radiographs [5, 6] and the findings may inform treatment change and optimisation. An early radiographic change in RA is peritellar osteopenia [7]. Early bone mineral density loss is a predictor of differentiation to RA in undifferentiated arthritis [8] and also predicts future joint damage in RA [9]. Plain radiographs have the limitation that they do not assess synovitis and bone
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