

**RHEUMATOID ARTHRITIS: BONE EROSIVE DAMAGE OVER
TIME**

**A LONGITUDINAL EVALUATION OF BONE EROSIVE DAMAGE IN THE
METACARPOPHALANGEAL JOINTS OF PATIENTS WITH RHEUMATOID
ARTHRITIS USING EARLY EROSIONS IN RHEUMATOID ARTHRITIS
(EERA) SOFTWARE**

By MICHAEL A. TOMIZZA, B.Sc.

A Thesis Submitted to the School of Graduate Studies in Partial Fulfilment of the
Requirements for the Degree Master of Science

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McMaster University MASTER OF SCIENCE (2015) Hamilton, Ontario (Medical Sciences)

TITLE: A Longitudinal Evaluation of Bone Erosive Damage in the Metacarpophalangeal Joints of Patients with Rheumatoid Arthritis Using Early Erosions in Rheumatoid Arthritis (EERA) Software AUTHOR: Michael A. Tomizza, B.Sc. (McMaster University) SUPERVISOR: Dr. Jonathan D. Adachi NUMBER OF PAGES: xiii, 130

In this study, the hands of patients with rheumatoid arthritis (RA) were assessed using magnetic resonance imaging (MRI) to investigate how erosive damage to the bone changes over time. Specialized computer software entitled Early Erosions in Rheumatoid Arthritis (EERA) was used to perform this analysis. Firstly, change in erosive damage was not found to be related to change in functional ability (e.g. eating, grip, etc.). Secondly, it appeared that individuals who demonstrated improvement in bone damage over time had significant damage at the beginning of the study period. Overall, this study provides new information for researchers and clinicians in terms of how this unique software can be used to enhance our understanding of RA. Future studies will continue to explore ways in which this software can be applied to address questions that are important to RA patients.

Abstract

In this longitudinal pilot study, magnetic resonance imaging (MRI) and Early Erosions in Rheumatoid Arthritis (EERA) software were used to quantify bone erosive damage in the metacarpophalangeal (MCP) 2-5 joints of the worst-affected hand (i.e. greatest swelling and tenderness at baseline) of patients with rheumatoid arthritis (n=35). Firstly, Spearman's rho (r_s) was used to evaluate the correlation between total change in sum erosive damage and change in functional ability, as well as the correlation between rate of change in sum erosive damage and change in functional ability. The r_s (p-value) for total change and rate of change in sum erosive damage was 0.099 (0.585) and 0.104 (0.565), respectively. Therefore, the null hypothesis that neither variable was associated with change in functional ability could not be rejected. Participants were also classified into three groups based on total change in sum erosive damage (improvement, stable or progression) and were examined for possible differences in a variety of measures using an exploratory, non-statistical approach. Most notably, participants in the improvement group had more than five times the mean sum erosive damage at baseline compared to the progression group and also appeared to be the least aggressively medicated of the three cohorts. This study is the first to apply EERA in a way that helps to address clinically important questions related to change in erosive damage and functional ability. Future studies should use the ideas and concepts generated in this pilot study to further explore the use of this highly reproducible erosion quantification software, with the ultimate goal of expanding the applications of EERA in both the research and clinical settings.

Acknowledgements

I would like to thank my supervisor, Dr. Jonathan D. Adachi, for all of his dedication and guidance during this Master's thesis. Dr. Adachi allowed me to take charge of this project and grow as a researcher and as an individual, while providing a wealth of advice along the way. I feel extremely fortunate to have learned from him. I would also like to thank my remaining supervisory committee members, Dr. Karen Beattie, Dr. Lawrence Hart and Dr. Christopher Gordon, for their knowledge and insight throughout this research project. Their broad combination of professional backgrounds and areas of expertise added greatly to the comprehensiveness of this project and I am very thankful for their contributions.

In addition, I would like to thank Dr. Adachi's administrative and research staff for all of their assistance and for making me feel welcome. Thank you to Christine Fyfe for training me to perform magnetic resonance imaging scans and to conduct study visits. Thank you to Dr. George Ioannidis, Dr. Arthur Lau and Dr. Andy Wong for providing input and direction. And thank you to Matthew Jessome for training me to use EERA software and for taking the time to see this project come to fruition.

Finally, I would like to thank the study participants for their time and contributing to the advancement of rheumatoid arthritis knowledge and understanding. I would also like to thank my family and friends for their unwavering support; accomplishments mean so much more when you have special people in your life to share them with. Thank you.

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List of Abbreviations

+FS: Fat Saturated
-FS: Non Fat Saturated
2-D: 2-Dimensional
3-D: 3-Dimensional
3DGE: 3-Dimensional Gradient Echo
ACPA: Anti-Citrullinated Protein Antibodies
ACR: American College of Rheumatology
AICAR: Aminoimidazole Carboxamide Ribonucleotide
Anti-CCP: Anti-Cyclic Citrullinated Peptides
BME: Bone Marrow Edema
CI: Confidence Interval
COX: Cyclooxygenase
CRP: C-reactive Protein
CT: Computed Tomography
DAS28: Disease Activity Score with 28-Joint Count
DMARD: Disease-Modifying Antirheumatic Drug
EERA: Early Erosions in Rheumatoid Arthritis
EMR: Electronic Medical Record
ESR: Erythrocyte Sedimentation Rate
EULAR: European League Against Rheumatism
FOI: Feature of Interest
FSE: Fast Spin Echo
HAQ-DI: Health Assessment Questionnaire- Disability Index
HR-pQCT: High-Resolution Peripheral Computed Tomography
ICC: Intraclass Correlation Coefficient
IgG: Immunoglobulin G
IL: Interleukin
IQR: Interquartile Range
MCP: Metacarpophalangeal
MID: Minimally Important Difference
MRI: Magnetic Resonance Imaging
MRx: Study Code Associated with Baseline Data Collection
MTP: Metatarsophalangeal
MTX: Methotrexate
NSAID: Non-Steroidal Anti-Inflammatory Drug
OPG: Osteoprotegerin
PIP: Proximal Interphalangeal
pMRI: peripheral Magnetic Resonance Imaging
PRO: Patient Reported Outcome
 r_s : Spearman's rho
RA: Rheumatoid Arthritis

List of Abbreviations (continued)

RAMRIS: Rheumatoid Arthritis Magnetic Resonance Imaging Scoring system
RANK: Receptor Activator of Nuclear factor Kappa B
RANKL: Receptor Activator of Nuclear factor Kappa B Ligand
RCT: Randomized Controlled Trial
RF: Radiofrequency
RhF: Rheumatoid Factor
SD: Standard Deviation
T: Tesla
T1w: T1-Weighted Image
T2w: T2-Weighted Image
TNF- α : Tumour Necrosis Factor alpha
vdHSS: van der Heijde-modified Sharp Score

Declaration of Academic Achievement

The Master of Science candidate, Michael Tomizza, is the primary author and lead contributor to this thesis. This project was a longitudinal study, with the Master of Science candidate responsible for preparing and executing the follow-up study visits. From September 2013 to June 2015, he was responsible for completing a literature review, study design (including the creation of study objectives and corresponding study questions), ethics approval, contacting past study participants for follow-up recruitment and providing informed consent, scheduling of study visits, data collection (including performing magnetic resonance imaging scans), data analysis and manuscript preparation. The contents of this thesis may form the basis for future publications in peer-reviewed scientific journals.

As this Master's research project was a follow-up study, another lead investigator, Ruben Tavares, performed data collection at baseline. Design of the follow-up study visit was closely based on pre-existing frameworks put in place at baseline. Other significant contributors to this dissertation include: Dr. Jonathan D. Adachi, the thesis supervisor who provided funding for the project and oversight throughout the research process, Dr. Karen Beattie, Dr. Lawrence Hart and Dr. Christopher Gordon, who served as the remaining members of the supervisory committee and offered guidance and support, Dr. George Ioannidis, who acted as consultant for overall statistical analysis and Matthew Jessome, who performed baseline analysis of magnetic resonance images and provided training in the use of Early Erosions in Rheumatoid Arthritis (EERA) software.

Chapter One: Overview of Rheumatoid Arthritis

1.1 Clinical Manifestation, Epidemiology and Economics

Rheumatoid arthritis (RA) is a severely debilitating autoimmune disease due to its chronic, systemic and inflammatory nature [1]. The primary site of inflammatory attack in RA patients is the synovial membrane, a soft tissue lining the synovial cavity of the joint [1]. Thus, joint pain and swelling are two of the major manifestations of RA, characterized by a symmetric distribution usually involving small joints of the hands and feet, such as the metacarpophalangeal (MCP), proximal interphalangeal (PIP) and metatarsophalangeal (MTP) joints [1]. Larger joints, such as the elbow and knee, may also become affected as the disease progresses [1]. These features will often cause patients to complain of morning stiffness lasting more than an hour and limit them in their abilities to perform even simple daily tasks, such as turning a doorknob or opening a jar [1].

In North America and Europe, the prevalence of RA is estimated to be 0.50 to 1.00% and annual incidence is approximately 0.02 to 0.05%, with age of onset highest in the fifth decade of life [2]. The prevalence is higher in Native American populations and lower in certain African populations, which suggests genetic and environmental roles in the etiology of RA [2], [3]. This multifactorial hypothesis is confirmed by the presence of multiple risk factors for RA spanning genetic, environmental, lifestyle and demographic traits [2]. For example, females have a higher risk of disease by approximately two to three times and smoking is also associated with an increased risk of RA [2], [4]. RA is

associated with a 48% and 60% increased risk of cardiovascular disease morbidity and mortality, respectively [5]–[7]. Overall, patients with RA experience a 3-10 year reduction in survival, depending on their age of onset and disease severity [2].

RA is the most common form of inflammatory arthritis and comes with a large financial burden [1], [8]. The cost per patient year in Canada is estimated to be \$19,000 and annual costs accrued to RA are estimated to be approximately \$5.5 billion [8], [9]. Short-term indirect costs related to work disability and long-term direct costs related to hospitalization and joint replacement surgeries are the two major expenses associated with the condition [10], [11].

1.2 Pathophysiology of Rheumatoid Arthritis

1.2.1 Outside-In vs. Inside-Out: Synovitis and Bone Marrow Edema

While RA pathophysiology is rooted in impaired immunological processes, the chronology of its pathogenesis is somewhat convoluted. Schett and Firestein outline the two pathogenic frameworks for RA using the terms “outside-in” and “inside-out” [12]. The traditional viewpoint is the “outside-in” hypothesis. In this construct, the synovial membrane lining diarthrodial joints acts as the origin of the inflammatory assault [12]. The process of establishing an inflammatory synovial environment is driven by both predetermined and stochastic events, possibly led by a network of serum cytokines and acute phase reactants, such as C-reactive protein (CRP) [12], [13]. This inflammation of the synovial tissue is referred to as synovitis, with synovial fibroblasts and monocytes enhancing the release of cytokines and matrix-degrading enzymes [14], [15]. Under the

outside-in hypothesis, the invasive and inflamed synovium activates disease progression by serving as a precursor for bone marrow edema (BME) [16], [17]. BME is characterized by a substitution of fatty marrow for an inflammatory mixture of T cells, B cells, plasma cells and osteoclasts, with the synovium acting as the source of these cellular mediators [18], [19]. Support for this hypothesis has been generated by studies demonstrating the ability of inflammatory synovial cells to degrade joint cartilage and promote osteoclast differentiation [20], [21]. These processes facilitate a route of entry from the synovium into the bone marrow by destroying the thin barrier of cartilage and cortical bone that separates the two compartments [12], [20].

In contrast to the traditional outside-in hypothesis, an alternative framework has emerged that labels BME as the initiator of RA pathogenesis, rather than the follower. Under the “inside-out” hypothesis or bone-marrow centred model of RA, enrichment of water and reduction of fat in the bone marrow, termed osteitis, occurs first [12], [22]. The enhanced composition of water and lymphocytes in the bone marrow leads to destruction of the cortical bone and invasion of pathological mediators into the synovium via enlarged bone channels, including the bone canaliculi [12], [17], [23]–[25]. This framework is supported by multiple immunological studies reporting immune activation of the bone marrow in RA patients, including an abundance of mature B cells and activated T cells, local expression of proinflammatory cytokines, such as tumour necrosis factor alpha (TNF- α), interleukin 6 (IL-6) and IL-8 and the heightened potential of bone marrow CD34 cells to form endothelial cells and assist in synovial vascularization [26]–

[28]. In section 1.2.2, further research regarding the roles and relationship between synovitis and BME will be discussed in the context of bone erosions.

1.2.2 Formation of Bone Erosions and the Roles of Synovitis and Bone Marrow Edema

Formation of bone erosions is a significant pathophysiological event in RA, with 20-50% of patients developing erosive damage in the first three years of disease activity and values exceeding 75% in certain cohorts [29]–[32]. Bone remodeling is a normal physiological process and involves a balance between bone formation, mediated by osteoblasts, and bone resorption, mediated by osteoclasts. In RA, this homeostasis shifts towards bone resorption. The interaction between the receptor activator of nuclear factor kappa B (RANK) and its ligand (RANKL) is a major target for disruption of bone remodeling [33]. When RANKL binds to RANK, which is expressed on the cell surface of osteoclast precursors and mature osteocytes, the signaling promotes osteoclast differentiation [34], [35]. Osteoprotegerin (OPG) acts as an inhibitory complement to this pathway by binding to RANKL and suppressing osteoclastic bone resorption [36], [37]. Therefore, it is the balance between RANKL and OPG that determines the degree of osteoclast activity and proliferation [34]. Under standard physiological conditions, osteoblasts are usually the main producer of RANKL [33]. However, elevated levels of proinflammatory cytokines found in RA pathology, such as TNF- α , IL-1, IL-6, IL-17, IL-21 and IL-23, upregulate the expression of RANKL and/or increase the sensitivity of RANK to RANKL [33], [38]–[49]. Fibroblast-like synoviocytes also begin to produce RANKL in larger quantities than osteoblasts [33]. Collectively, these processes shift the ratio of RANKL:OPG towards RANKL and thus promote osteoclast activation and

subsequent bone destruction. While certain studies have suggested that TNF- α , IL-1 and IL-6 can activate osteoclasts independently of RANKL, it appears that a minimum level of RANKL is necessary for these cytokines to exert their osteoclastogenic effects [50]–[54].

The roles of synovitis and BME are further delineated when discussing erosion formation. A study conducted by Conaghan *et al.* assessing patients with early RA found that erosions did not form in joints where synovitis was absent, required a synovitis threshold (i.e. minimum synovial thickness) to be reached before developing and were correlated with the degree of synovial inflammation [55]. Other studies have supported the ability of synovitis to predict erosion development and cortical breaks have been found to form preferentially in locations close to synovial membrane insertion sites [16], [56], [57]. However, as was the case when discussing the two different RA hypotheses, certain studies have brought BME to the forefront of erosive disease. Haavardsholm *et al.* found that BME predicted erosive progression in a subset of RA patients followed for a year, while synovitis did not [58]. Hetland *et al.* also found BME to be the strongest predictor of erosive disease over a two-year period and McQueen *et al.* found similar results over a six-year period [59], [60]. Lastly, Mundwiler *et al.* reported that the absence BME nearly guaranteed that a bone erosion would not develop over a one-year period [61]. Taken together, these data suggest that while the sequence of events involved in erosion formation is still speculative, BME may cause erosions both directly through subchondral bone damage and indirectly through migration of inflammatory infiltrates

into the joint cavity and subsequent synovitis. Regardless, synovitis and BME clearly play important roles in the development of bone erosions.

1.3 Diagnosis

Many biological markers are used in clinical care of patients with RA as a means of providing further information for diagnostic and prognostic purposes. Four of the most commonly used biomarkers are erythrocyte sedimentation rate (ESR), CRP, rheumatoid factor (RhF) and anti-cyclic citrullinated peptide (anti-CCP). ESR and CRP are markers of inflammation and are elevated in the majority of patients experiencing active disease, although 35% to 45% of patients may have normal levels upon presentation [62].

Elevated ESR and CRP are associated with radiographic progression of disease and levels have been found to decrease during clinical trials with therapeutic agents [63], [64]. RhF and anti-CCP differ from ESR and CRP in that they are autoantibodies. RhF is an antibody for the Fc portion of immunoglobulin G (IgG) and is elevated in 70 to 85% of RA patients throughout the course of their disease [1], [65]. Positivity for RhF (> 45 IU/mL) has a sensitivity and specificity of approximately 66% and 82%, respectively, for the diagnosis of RA [1]. Positivity for RhF may also indicate a poor prognosis reflected through aggressive structural damage [1], [66]. Anti-CCP is an antibody that targets citrullinated proteins and belongs to the family of anti-citrullinated protein antibodies (ACPA). Anti-CCP has a similar sensitivity (70%) but a higher specificity (95%) than RhF for the diagnosis of RA [1]. As with RhF, elevated anti-CCP is also associated with an unfavourable prognosis in RA [1]. The effects of RhF and anti-CCP may be additive [66]–[70].

In 1987, the American Rheumatism Association, now the American College of Rheumatology (ACR), created the following criteria for the diagnosis of RA and published the guidelines in 1988. [71]. To be diagnosed with RA, a patient was required to meet four of the following seven criteria, with items 1 to 4 only being met if relevant symptoms were present for at least six weeks:

- 1) Morning stiffness (in and around the joints, lasting at least 1 hour before maximal improvement)
- 2) Arthritis of three or more joint areas (\geq three joint areas simultaneously have had soft tissue swelling or fluid – not bony overgrowth alone – observed by a physician. The fourteen possible areas are right or left PIP, MCP, wrist, elbow, knee, ankle and MTP joints)
- 3) Arthritis of the hand joints (at least one swollen area, as defined above, in a wrist, MCP or PIP joint)
- 4) Symmetric arthritis (simultaneous involvement of the same joint areas, as defined in item 2, on both sides of the body; bilateral involvement of the PIPs, MCPs or MTPs is acceptable without absolute symmetry)
- 5) Rheumatoid nodules (subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxta-articular regions, observed by a physician)
- 6) Serum rheumatoid factor (demonstration of abnormal amounts of serum factor by any method for which the result has been positive in $<5\%$ of normal control subjects)

- 7) Radiographic changes (radiographic changes typical of rheumatoid arthritis on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal body decalcification localized in or most marked adjacent to the involved joints – osteoarthritic changes do not qualify)

While the 1987 ACR criteria were well received in their ability to discriminate defined, established RA from other rheumatologic conditions, they suffered from a major limitation. A paradigm shift occurred in RA clinical care, fueled by advances in therapeutic drugs and medical imaging, which shifted the focus from *reactive* care (i.e. treating erosive disease) to *proactive* care (i.e. preventing erosive disease from occurring). Therefore, a new set of criteria was required with a focus on identifying RA early in the disease process to avoid adverse outcomes. In 2010, the ACR and the European League Against Rheumatism (EULAR) developed new classification criteria for RA [72]. These criteria required the presence of synovitis in at least one joint and the absence of an alternative diagnosis that offered a more suitable explanation for the synovitis. As outlined in Table 1.1, a scoring system was developed where a total of 6 or greater out of 10 is required for classification as “definite RA.”

Table 1.1 The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis.

Criterion	Score
<i>A. Joint Involvement</i>	
1 large joint	0
2 – 10 large joints	1
1 – 3 small joints (with or without involvement of large joints)	2
4 – 10 small joints (with or without involvement of large joints)	3
> 10 joints (at least 1 small joint)	5
<i>B. Serology (at least 1 test result is needed for classification)</i>	
Negative RhF <i>and</i> negative ACPA	0
Low-positive RhF <i>or</i> low-positive ACPA	2
High-positive RhF <i>or</i> high-positive ACPA	3
<i>C. Acute-phase reactants (at least 1 test result is needed for classification)</i>	
Normal CRP <i>and</i> normal ESR	0
Abnormal CRP <i>or</i> abnormal ESR	1
<i>D. Duration of Symptoms</i>	
< 6 weeks	0
≥ 6 weeks	1

ACPA: anti-citrullinated protein antibodies. CRP: C-reactive protein. ESR: erythrocyte sedimentation rate. RhF: rheumatoid factor.

1.4 Treatment

Many medication options exist for the treatment of patients with RA, with the ultimate goal of minimizing disease activity [73], [74]. An overview of the main drug classifications are outlined in Sections 1.4.1 through 1.4.3, followed by an outline of treatment strategies and efficacies in Section 1.4.4.

1.4.1 Disease-Modifying Antirheumatic Drugs

Disease-modifying antirheumatic drugs (DMARDs) represent the current frontline therapy for RA. Methotrexate (MTX), a folic acid analogue, is recognized as the first line DMARD for RA due to its safety, efficacy and cost effectiveness [75]. MTX, specifically its polyglutamated metabolite, inhibits the enzyme aminoimidazole carboxamide ribonucleotide (AICAR)-transformylase [76]. This inhibition leads to an increase in adenosine concentration in the extracellular space. It is hypothesized that the anti-inflammatory effects of MTX are mediated through reduced leukocyte adhesion to endothelial cells caused by the accumulation of adenosine [77]. While this anti-inflammatory mechanism is supported in the literature, several other pathways have been proposed, including reduction of antigen-dependent T-cell proliferation, promotion of T-cell apoptosis and manipulation of cytokine production [78]. MTX is usually administered orally – but can also be given subcutaneously or intramuscularly – on a weekly basis, with doses varying from 7.5 to 25 mg [79]. Folic acid is prescribed to help offset folate deficiency caused by MTX administration and regular laboratory testing is recommended (e.g. to monitor liver and kidney function) [76], [79].

Leflunomide is another DMARD and shares many similarities with MTX. Like MTX, the therapeutic actions of leflunomide are mediated via a metabolite [79]. Leflunomide disrupts nucleic acid synthesis by inhibiting an enzyme responsible for the formation of pyrimidine nitrogenous bases [79]. This inhibition leads to a reduced proliferation of lymphocytes, making it a useful immunosuppressant for the treatment for RA. Leflunomide is administered orally (10-20 mg/day) and patients should be monitored closely for potential side effects via laboratory testing, similar to MTX [79].

Two other commonly used DMARDs are sulfasalazine and hydroxychloroquine. Sulfasalazine provides both anti-inflammatory and immunomodulatory effects via 5-aminosalicylic acid and sulfapyridine, while hydroxychloroquine is an antimalarial that is believed to down-regulate the immune response through disruption of the antigen-processing ability of antigen-presenting cells, such as macrophages [76], [79], [80]. Both drugs are given orally, with a 2-3 g/day dose for sulfasalazine and a 400 mg/day dose for hydroxychloroquine [79]. Gastrointestinal side effects are sometimes seen with both drugs and patients taking hydroxychloroquine should be monitored for ocular toxicity [79], [81], [82].

1.4.2 Biologic Response Modifiers

Biologic response modifiers, or biologics, represent a class of drugs with specific immunological targets and are sometimes considered as a specialized subclass of DMARDs. Pharmacological agents that block TNF- α comprise the major subgroup of biologic response modifiers. These agents include adalimumab, certolizumab pegol, etanercept, golimumab and infliximab, all of which bind to TNF- α to exert their inhibition

[79]. Other forms of biologics include inhibitors of T-lymphocytes (abatacept), monoclonal antibodies that bind and destroy B cells (rituximab) and blockers of IL-6 (tocilizumab) [79]. Collectively, the biologic agents act to suppress excessive autoimmune activity in patients with RA, thus resulting in decreased disease activity. Doses and administration vary depending on the biologic, with subcutaneous or intravenous routes commonly used [79]. However, use of biologics comes at a price, both financially and immunologically. Firstly, costs may range from \$15,000 to \$25,000 a year and insurance providers may require documentation of conventional DMARD treatment failure before agreeing to cover the more expensive biologic options [79]. Secondly, given the direct inhibition of signaling molecules integral to the immune system, risk of serious infections is a concern [75].

1.4.3 Non-Steroidal Anti-Inflammatory Drugs and Corticosteroids

Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit cyclooxygenase (COX) enzyme subclasses I and II, which causes a reduction in prostaglandin-mediated inflammatory activity [83]. A variety of NSAIDs are available for clinical use in RA, including celecoxib, diclofenac and naproxen, among others. These drugs are usually taken daily, with doses varying according to brand [79]. While NSAIDs were once considered frontline therapy for RA due to their ability to provide relief of pain and inflammation, two major concerns emerged. Firstly, despite their analgesic effects, NSAIDs do not address the underlying disease processes driving RA pathophysiology [84], [85]. Secondly, NSAIDs are associated with an increased risk of gastrointestinal and cardiovascular side-effects [86]–[88].

Similar to NSAIDs, corticosteroids offer anti-inflammatory benefits to patients with RA. Corticosteroids, such as prednisone, represent a class of adrenal hormones that provide symptomatic relief and can be given orally or intra-articularly [79]. Although there is mixed evidence of their impact on disease progression, a Cochrane review published in 2007 suggests that corticosteroids are effective at reducing the rate of erosive damage when given in combination with other medication, such as DMARDs [89]. However, as with NSAIDs, orally-administered corticosteroids are associated with a spectrum of adverse effects [79], [86].

1.4.4 Treatment Strategy

The timely commencement of treatment in RA is often referred to as the “Window of Opportunity,” which has been suggested as the first three months of symptom onset [90]. Thus, the standard treatment strategy for RA involves initiating an aggressive regimen of DMARDs early in the disease process [79]. The “treat-to-target” approach, in which therapeutic goals focus on remission or low disease activity, emerged from the results of a 2004 randomized controlled trial (RCT) led by Grigor *et al.* and has been scrutinized over the last decade [75], [91]. Researchers found that patients who received intensive care (i.e. protocol outlining a sequential combination DMARD therapy plan) experienced greater improvements in disease activity levels and less radiographic progression compared to those receiving routine care (i.e. no standard protocol and only use of DMARD monotherapy). Other studies have also reported that aggressive treatment with combination DMARDs resulted in remission or low disease activity, as well as

positive clinical and radiological long-term outcomes [92]–[95]. In terms of biologic therapy, multiple studies have assessed the effectiveness of combination regimens consisting of only DMARDs (i.e. MTX + sulfasalazine + hydroxychloroquine) in comparison to combination regimens consisting of a single DMARD and additional biologic therapy (i.e. MTX + infliximab) [96]–[100]. Improvements in disease activity levels and proportions of patients in remission were largely similar in both groups, although inclusion of biologic therapy resulted in lower radiographic progression of disease [98]. Repair of erosions has also been reported in patient groups prescribed various DMARD combination regimens, some including biologic agents and some only consisting of DMARDs alone [101]–[104]. While treatment approaches could potentially depend on whether the patient is drug naïve or has failed initial MTX monotherapy, combination DMARDs may be just as effective as regimens using biologic agents [75]. Ultimately, the optimal treatment strategy should be tailored to the individual patient’s prognostic profile, as well as their goals and expectations [75], [79], [82].

1.5 Measures of Disease Activity and Functional Ability

Many clinical and patient-reported outcome (PRO) measures exist in the field of RA. These indicators allow physicians and researchers to evaluate overall disease activity and treatment efficacy and to assess whether changes in status have translated into tangible effects on the patient’s activities of daily living [105]. Two of the most commonly used measures in both the clinical and research settings are the Disease Activity Score with 28-joint count (DAS28) and the Health Assessment Questionnaire-Disability Index (HAQ-DI), which are discussed in Section 1.5.1 and 1.5.2.

1.5.1 Disease Activity Score with 28-Joint Count

The DAS28 is considered the gold standard for assessing disease activity in RA and has been endorsed by the ACR and EULAR for use in clinical trials [106]–[108]. The DAS28 consists of four main components: a swollen joint count of the bilateral shoulders, elbows, wrists, MCPs, PIPs and knees, a tender joint count at the same locations, a blood measurement (ESR or CRP) and a patient global health assessment measured on a visual analog scale. A three-variable version of the DAS28, which omits the patient global health assessment, can also be used. After inputting values into the algorithm, a score is generated ranging from 0.00 to 9.71, with 0.00 indicating inactivity and 9.71 indicating very active disease. Validated criteria also exist that allow physicians to make disease activity interpretations at a single point in time or over multiple DAS28 measures, with guidelines in place to categorize treatment responsiveness and remission [109].

1.5.2 Health Assessment Questionnaire- Disability Index

The HAQ-DI is an instrument used to determine PROs of disease and is the gold standard for measuring functional status in RA [110]–[115]. While the HAQ-DI is not disease-specific, the original report outlining the questionnaire is one of the most cited papers in rheumatology and has been used extensively in the field of RA [110], [113]. The HAQ-DI focuses on identifying limitations associated with carrying out daily activities, such as eating and walking. Questions are categorized under eight disability items and are scored from values of 0 (without any difficulty) to 3 (unable to do). The item subscores are then averaged to produce a final HAQ-DI score ranging from 0 to 3,

with 0 being the most favourable. Researchers and clinicians can use the minimally important difference (MID) when assessing change over time to determine the smallest difference in the HAQ-DI that a patient would classify as meaningful change [116], [117]. Reported MIDs for the HAQ-DI vary from -0.19 to -0.24 for improvement and +0.49 for worsening [118]–[121]. However, it was found that the MID for the HAQ-DI is smaller in RA clinical practice than in RCTs, with values for improvement and worsening estimated at -0.09 and +0.15, respectively [122]. Possible explanations for this discrepancy between the clinical care and RCT MIDs include differences in disease activity, treatment effectiveness and patient expectations [122], [123].

Chapter Two: Medical Imaging in Rheumatoid Arthritis

Various medical imaging modalities and techniques can be used to assess all three major physiological events associated with RA: synovitis, BME and bone erosions. Detection of erosions through medical imaging serves two important roles. Firstly, emphasis is now placed on identifying RA early in the disease process prior to substantial erosive damage, as seen through the 2010 ACR/EULAR diagnostic criteria for RA [72]. Diagnostic imaging can aid in identifying and characterizing erosive damage early in the disease process before substantial progression occurs. Secondly, bone erosions can be monitored as part of clinical practice and clinical trials to evaluate treatment efficacy [79]. Different imaging modalities allow for visualization of various disease characteristics, each with its own advantages and disadvantages. A brief introduction of the main modalities that are used to image RA are outlined in this chapter, with emphasis placed on magnetic resonance imaging (MRI).

2.1 Radiography

Radiography, or X-ray, has the benefit of being simple, affordable and accessible and can be used for diagnosis and treatment monitoring [124]. Additionally, a scoring system exists that allows for semi-quantification of bone erosions, as well as joint space narrowing, on an ordinal scale [125]. However, X-ray has significant limitations. Radiography presents a 2-dimensional (2-D) image of 3-dimensional (3-D) anatomy, cannot capture inflammatory changes to non-osseous tissue that usually occur early in the

disease process (e.g. synovitis and bone marrow edema) and is not able to detect early bone erosions with the same sensitivity as other modalities [126]–[129]. Given the importance of identifying and tracking erosions in the early stages of disease, radiography, though valuable, is not a comprehensive tool for evaluating RA.

2.2 Ultrasound

Ultrasound has a distinct set of characteristics that make it a useful modality for understanding RA. Ultrasound operates through the visualization of blood flow and thus is able to depict soft tissue changes, including the vascular changes associated with synovitis and tenosynovitis, an inflammation of tendons sometimes seen in RA patients [130], [131]. Ultrasound can also be used to identify bone erosions and is more sensitive than radiography at erosion detection [128]. However, ultrasound is largely operator-dependent and unified scoring systems for synovitis and bone erosions are lacking [132]. Further development of the application of ultrasound in the RA population for evaluating erosive damage is warranted and may prove to be influential in both the research and clinical settings.

2.3 Computed Tomography

Computed tomography (CT), which employs a tomographic visualization technique, is able to very clearly delineate erosions due to their diminished signal compared to other nearby sources (e.g. the cortex and trabecular bone) [126], [133]. The major obstacle to use of CT in the clinical setting is intense radiation exposure. Current research involving CT aims at finding methods to reduce radiation exposure and

peripheral devices have recently been studied that allow for sensitive detection of small erosions [134]. Outside of erosion detection, CT lacks the ability to depict soft tissue changes, such as synovitis and BME. This technical limitation hinders the applicability of CT for the evaluation of early RA [126].

2.4 Magnetic Resonance Imaging

2.4.1 Overview

MRI has emerged as a favourable modality for understanding RA [135]–[137]. MRI provides more visual information than radiography due to its multi-slice imaging technique, can depict soft tissue change that are predictive of bone erosions (i.e. synovitis and bone marrow edema) and it is more sensitive than radiography at detecting erosions early in the disease process [56], [126], [129], [138]. The advantages of MRI make it an attractive modality in the research setting. Peterfy *et al.* published a review highlighting the “coming of age” of MRI onto the clinical trial scene, citing seven RCTs that used MRI to assess the influence of various drug therapies on the progression of erosions [103], [136], [139]–[144]. Additionally, the shift towards use of active comparators instead of placebos has minimized the differences in therapeutic outcome measures (e.g. erosive progression) between groups in RCTs [79], [136]. Therefore, compared to radiography, MRI is advantageous due to the smaller sample sizes and shorter study windows required to detect and characterize treatment efficacy in terms of structural changes [136].

Like all imaging modalities, MRI does have limitations. The two major disadvantages to use of MRI in the clinical setting are limited accessibility and high costs

[145]. A possible solution to these issues has come in the form of peripheral MRI (pMRI) scanners, which scan only the anatomy of interest rather than the full body. This alternative offers lower purchasing costs, greater patient comfort, enhanced versatility and convenience and has been shown to correlate well with conventional full body scanners [145]–[148]. When conducting pMRI scans, the use of a small, tight-fitting coil around the anatomy of interest can help to reduce motion artifact and can improve the signal-to-noise ratio for the given unit by reducing the noise from areas outside of the field of view [149]. Like full body scanners, extremity MRI is also able to detect erosions with greater sensitivity than radiography [150].

2.4.2 General Imaging Principles

An overview of the basic imaging principles of MRI is summarized in this subsection based on a guide of MRI physics written by Evert J. Blink, which can be found at <http://www.mri-physics.net/bin/mri-physics-en-rev1.3.pdf>, as well as the Ph.D. dissertation of Patrick D. Emond [126]. The ability of an MRI scanner to formulate a 3-D image of the anatomy of interest is based on the composition of human tissue. Protons, or hydrogen atoms, are abundant in the human body. Each hydrogen atom has an individual magnetic field and is randomly spinning around an axis. An MRI scanner contains a large magnet, which runs horizontally and produces a stable magnetic field. The magnet contains a hollow tube where the patient or anatomy of interest can be inserted, which is referred to as the bore of the magnet. The unit used to indicate the strength of the magnet is referred to as a tesla (T), with clinical scanners generally varying from 0.1T – 3.0T.

When the patient is exposed to the magnetic field created by the MRI scanner, his/her hydrogen atoms line up facing opposing directions in a roughly even manner. However, certain atoms remain unmatched; they do not have a counterpart atom to pair with and thus do not cancel out. A radiofrequency (RF) system, consisting of a synthesizer, amplifier and transmitting coil, applies an RF pulse that is absorbed by the unmatched hydrogen atoms. This increase in energy causes the unmatched atoms to spin in a different direction. Simultaneously, small gradient magnets within the scanner turn on and off rapidly, which programs the local magnetic field and creates the “slices” of the image. Once the RF pulse is turned off, the unmatched atoms return to their original alignment and release the previously absorbed energy. A receiving coil captures the released energy, which comprises of two relaxation times, T1 and T2. T1 refers to the time required for the hydrogen atoms to realign in the longitudinal direction, whereas T2 refers to the time required for the decay of transverse magnetization.

Images can be acquired in any plane, depending on the feature of interest (FOI) and desired appearance. Magnetic resonance images can also be weighted in relation to T1 or T2 relaxation times. In T1-weighted (T1w) images, fat appears bright and water appears dark. In T2-weighted (T2w) images, water appears bright, while fat and bone appear black. Fat saturation can be applied to further suppress signal from fatty tissue. In relation to RA, T1w, non-fat saturated (-FS) images are ideal for characterizing bone erosions, which will appear as dark lesions due to the absence of fatty marrow [151]–[153]. Conversely, T2w, fat saturated (+FS) images can be used for assessing aqueous characteristics, such as synovitis or bone marrow edema [79]. Lastly, various RF pulse

sequences exist that vary in their ability to contrast different tissues. For example, fast spin echo (FSE) provides strong visualization of erosions due to the significant contrast between bright fatty bone and dark eroded lesions [154]. 3-D spoiled gradient echo (3DGE) is another RF pulse sequence that also provides suitable contrast for identifying and characterizing bone erosions, with the added benefit of a reduced scan time [126].

2.4.3 Rheumatoid Arthritis Magnetic Resonance Imaging Scoring System

An internationally recognized RA scoring system exists for evaluating MR images, referred to as the Rheumatoid Arthritis Magnetic Resonance Imaging Scoring system (RAMRIS) [152], [155]. RAMRIS includes semi-quantitative scoring components for synovitis, BME and bone erosions. Synovitis scores are calculated on an ordinal scale from 0 to 3, with 0 representing no synovitis and each subsequent unit increase representing a one third increase in maximum potential synovial swelling. BME is also scored on an ordinal scale from 0 to 3 according to the proportion of bone thought to be involved: 0= 0%, 1=1-33%, 2= 34-66%, 3= 67-100%. Lastly, erosions are assigned a score ranging from 0 to 10 based on the percentage of bone thought to be eroded. For example, a score of 2 indicates that 11 to 20% of the bone is estimated to be eroded. While having a unified scoring system makes MRI accessible for use in RA research, barriers exist that hinder the clinical practicality of RAMRIS, including the only partially quantitative nature of the scoring system, the lack of strong reader agreement when assigning scores, the large time requirements and the need for a trained professional to score images [156], [157]. Manual tracing of MRI-captured erosions can address some of these limitations, as it represents one of the closest quantitative estimates of bone

erosions, but it does not address the issue of lengthy analysis and requires proper training [126].

2.4.4 Early Erosions in Rheumatoid Arthritis Software

Given the emphasis on detecting erosions early in the disease process, there is an opportunity to improve the efficiency, accuracy and reliability of evaluating erosive damage. Computerized approaches for assessing erosive damage captured on different modalities, including MRI, have been developed [134], [158]–[160]. Early Erosions in Rheumatoid Arthritis (EERA) is an example of such software and was created by Patrick D. Emond at McMaster University in Hamilton, Ontario, Canada [126], [154], [161]. EERA provides a fully quantitative measure of erosion volume (mm^3) using T1w coronal images with a 3DGE sequence [161]. EERA is a hybridized semi-automated segmentation algorithm that comprises both region-growing and level-set techniques. Segmentation refers to the process of identifying and separating the FOI from surrounding tissues [126]. In this case, the FOI is a bone erosion. Multiple segmentation approaches exist, which vary in terms of their strengths and weaknesses. The region growing technique allows a reader to place a seed in a designated area and assesses similarity characteristics in order to determine distinct regions, which is useful when boundaries between the FOI and surrounding tissue are pronounced [126]. Region growing algorithms can distinguish erosion boundaries spanning multiple slices and are able to identify the boundaries between low signal bone erosions and high signal bone marrow, but struggle to distinguish boundaries between bone erosions and low-mid signals derived from synovium [126]. A second technique, level-set segmentation, uses

differences rather than similarities to distinguish boundaries, which is desirable when the FOI is not clearly delineated from the surrounding tissues [126]. Like region growing algorithms, the level-set technique is also able to identify erosion boundaries in multiple slices [126]. Whereas region-growing segmentation is able to distinguish erosion/marrow boundaries but not erosion/synovium boundaries, the level-set technique provides clear differentiation of erosion/synovium regions without the ability to establish differences in erosion/marrow regions [126]. Therefore, the hybridization approach of EERA draws on the strengths of both algorithms in order to maximize segmentation effectiveness and accommodate bone erosions of different contours.

The erosion segmentation process involves four steps. Firstly, the reader opens the EERA software and selects an MR image from a database. Once the image is loaded, the reader scrolls through the various slices to visually inspect for potential erosions in MCPs 2-5 (Figure 2.1). The first MCP joint of the thumb is not assessed because of its unique anatomy and challenges in capturing the joint during MRI scan acquisition [157]. The erosion definition established for EERA follows the guidelines set by RAMRIS and can be classified as a sharply marginated bone lesion accompanied by proper juxta-articular positioning and signal characteristics [152]. Lesions must also appear in at least three consecutive 1 mm slices in order to be considered an erosion [161]. Secondly, if an erosion is found, the reader places a seed point at the geometric centre of the erosion (Figure 2.2). Thirdly, the reader proceeds to run the segmentation consecutively to ensure that the seed has stabilized in the centre position. If re-running the segmentation process does not stabilize the seed, the reader simply redirects the seed as close to the geometric

centre as possible and does not re-run segmentation. Additionally, five algorithm parameter sets exist, with each varying in its erosion mapping properties. This feature allows a reader to cycle through the five parameter sets, labeled A through E, in order to determine which set provides the closest fit to the erosion boundaries (Figure 2.3). Lastly, once the reader feels satisfied with seed placement and parameter set selection, EERA provides a quantitative measure of erosion volume (mm^3) by multiplying erosion cross-sectional area by slice thickness (Figure 2.4). If the hand that is being evaluated contains more than one erosion (e.g. one erosion on MCP2 and one erosion on MCP3), the reader can repeat steps 1 through 4 for any remaining erosions and then sum the volumes to produce a sum erosive damage score. This convention has been used in past abstracts and recently accepted publications and will also be used in this dissertation [162]–[164] .

EERA addresses some of the drawbacks of both RAMRIS and manual segmentation. Firstly, it provides an actual erosion volume (mm^3) that correlates strongly with manual segmentation, whereas RAMRIS only provides a semi-quantitative rank of erosion size [161]. Secondly, EERA is a more reproducible means of assessing bone erosions compared to RAMRIS and other scoring methods. The intraclass correlation coefficient (ICC) is an indicator of the relative reliability of a measurement and can be used to investigate both *inter*-rater reliability (i.e. how close measurements are when performed by different readers) and *intra*-rater reliability (i.e. how close measurements are when performed by the same reader) [165]. Bird *et al.* evaluated the inter-rater reliability for both a computerized erosion volume assessment and RAMRIS [156]. Pre-training ICC values were 0.51 for the computerized erosion volume assessment and 0.61

for RAMRIS, which indicates moderate agreement. Even after training the readers in the two methods, ICCs only increased to 0.58 and 0.75, respectively. In comparison, studies attempting to determine ICCs for both inter- and intra-rater reliability of EERA have displayed excellent results, with a recently accepted manuscript by Tomizza *et al.* reporting ICCs (95% confidence interval, CI) of 0.976 (0.965 to 0.984) for inter-rater reliability and 0.996 (0.994 to 0.997) for intra-rater reliability [161]–[164]. Lastly, EERA improves on some of the practical issues involved in evaluating MRI-detected erosions. Analyzing erosions using RAMRIS or manual segmentation requires professional expertise, whereas EERA is relatively straightforward and has been shown to be reproducible when used by undergraduate and graduate students with no professional training [162]–[164]. EERA also improves on efficiency of analysis, with the manual segmentation process taking roughly three times longer to complete [161].

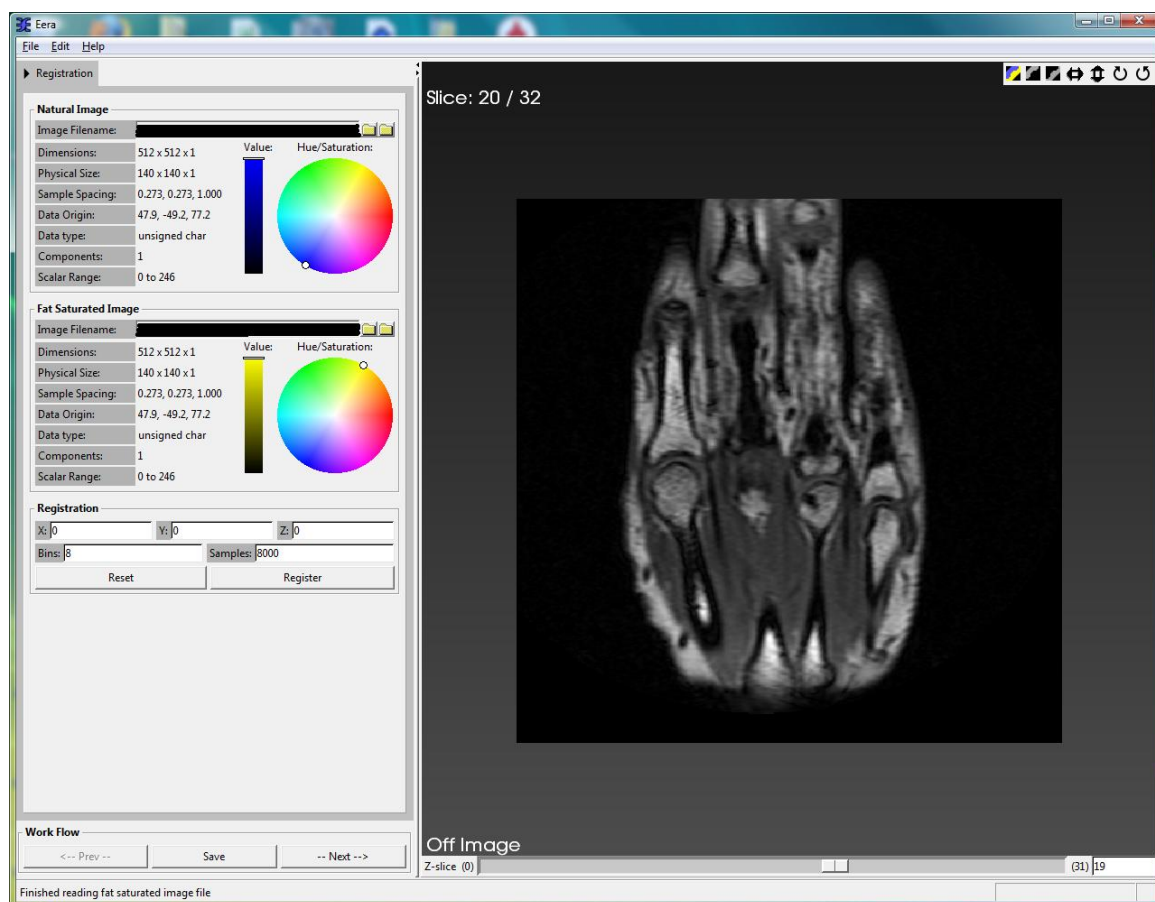


Figure 2.1: The reader opens EERA and loads an MR image from a database. In this example of a right hand, after scrolling through the slices the reader has found an erosion on the fourth metacarpal head.

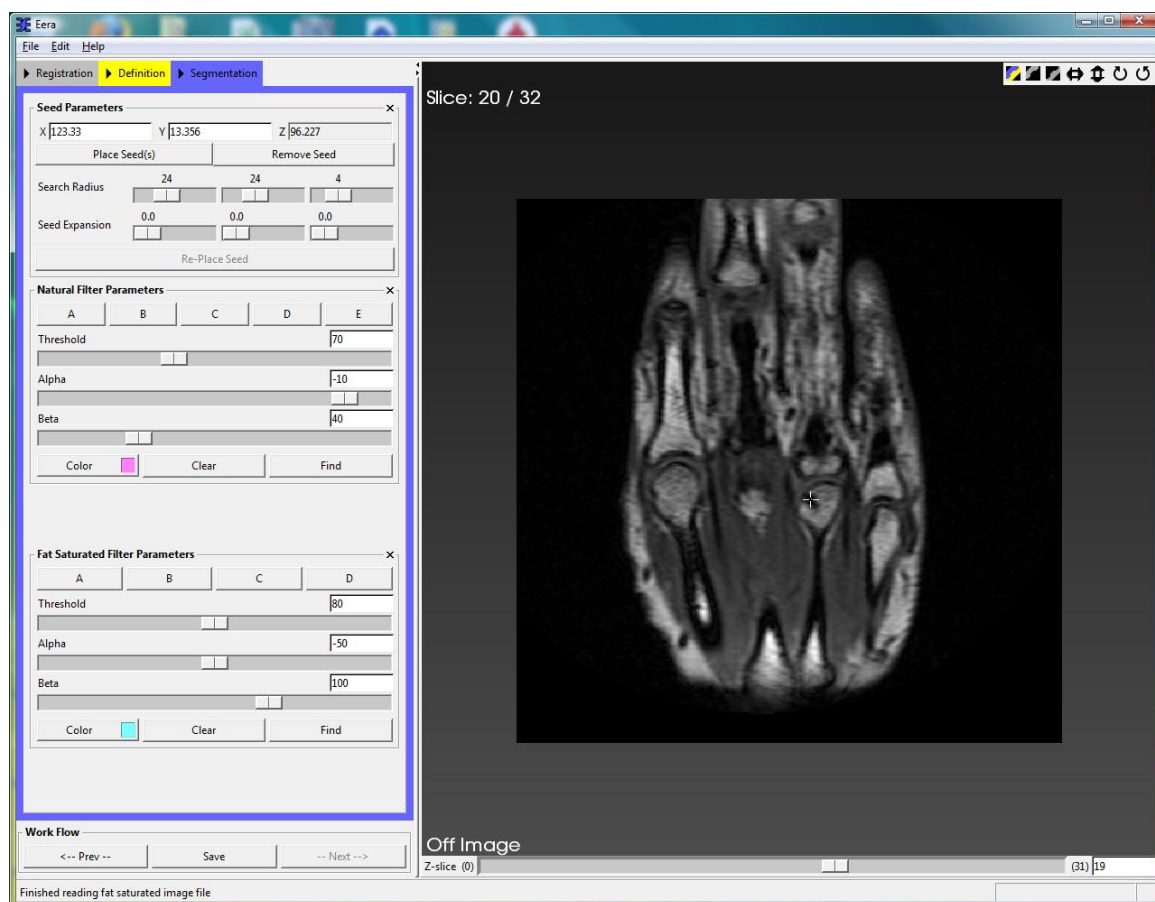


Figure 2.2: The reader places a seed point in the centre of the erosion, as seen by the white crosshairs found on the metacarpal head of MCP4.



Figure 2.3: The reader re-runs the segmentation process until the seed has ceased to shift positioning and has stabilized in the geometric centre. The reader also determines which of the five parameter sets, labeled A through E, provides the closest fit to the erosion boundaries, as seen by the white outline surrounding the erosion on the metacarpal head of MCP4.

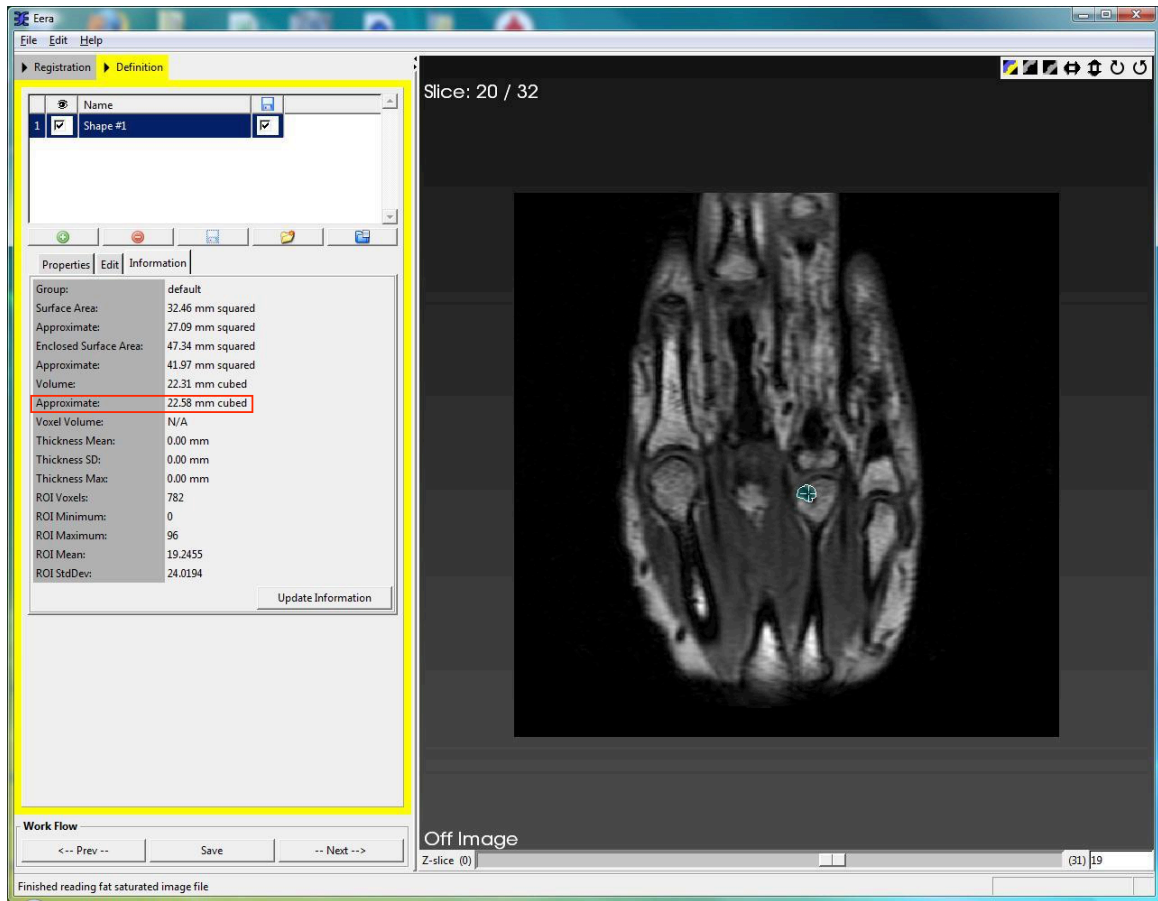


Figure 2.4: Once the reader is comfortable with the seed positioning and selected parameter set, EERA provides an estimation of the erosion volume (mm^3), as seen in the red box on the left panel of the figure. In this example, the estimated volume of the erosion is 22.58 mm^3 .

Chapter Three: Study Framework and Methodology

3.1 Study Overview and Rationale

With a patient-centred model of healthcare in place, the importance of PROs has emerged in both RA clinical trials and clinical practice [105], [166]. Functional ability, as measured by the HAQ-DI, is an example of an outcome that takes the patient's daily life into consideration. Various studies have investigated the link between structural joint damage and functional ability [167]–[170]. However, these assessments have relied heavily on X-ray evidence of bone damage. The superior capacity of MRI to detect erosions relative to X-ray makes it an ideal modality for such research, particularly given the recent diagnostic and therapeutic emphasis on preventing erosive disease [56], [72], [129], [138]. Additionally, it is not clear whether *total* change in erosive damage and *rate* of change in erosive damage differ in their association with change in functional ability. With EERA's capacity for providing a fully quantitative measure of erosion volume and producing a sum erosive damage score, a unique and important opportunity emerges for use of this software in a study investigating the association of both total change and rate of change in sum erosive damage with change in functional ability.

Exploring how erosive damage changes over time is a second potential research focus for the EERA software. Multiple studies have attempted to identify prognostic factors that are associated with or predict future erosive disease and structural damage [171]–[179]. Once again, these studies are largely limited by X-ray scoring techniques

that are semi-quantitative and not as sensitive to erosions as MRI. Use of EERA would provide a more practical approach and would allow for the stratification of patients based on total change in sum erosive damage over time (i.e. improvement, stable, progression), which could then be used to assess for possible differences among the three groups. The ultimate goal of such research is to provide criteria that could be used in clinical practice to identify how a patient's erosive damage may change over time.

The following Master's thesis study was framed around two Ph.D. projects. The first dissertation, entitled *Magnetic Resonance and Radiography in Rheumatoid Arthritis: Intermodality Comparisons of Erosion Detection*, compared the use of both MRI and X-ray for erosion detection and was led by investigator Ruben Tavares [79]. For simplicity, this project will hereafter be referred to as "MRx," reflecting the two modalities investigated. The MRI component of the study used a 1.0T OrthOne pMRI scanner (General Electric Healthcare, Wilmington, MA) to evaluate the MCP 2-5 joints in a cohort of patients with early RA and focused on the hand considered to be the worst-affected based on cumulative swollen and tender joint counts.

The second dissertation, *Bone Erosion Measurement in Subjects with Rheumatoid Arthritis Using Magnetic Resonance Imaging*, introduced a novel hybrid segmentation algorithm for the quantification of bone erosions detected on MRI and was led by investigator Patrick D. Emond [126]. This software, EERA, was discussed in Section 2.4.4.

This Master's thesis project is a prospective cohort study and uses the EERA software to conduct a longitudinal evaluation of bone erosive damage in a subset of

participants who were enrolled in the MRx study. The study received ethics approval from the Hamilton Integrated Research Ethics Board (HIREB). Combining the technological innovation of EERA with the pre-existing MRx framework was advantageous in many ways. Firstly, outside of a conference abstract assessing EERA reliability, a longitudinal analysis of erosive damage using EERA has not been performed and could provide stronger scientific evidence than a cross-sectional study [163]. Longitudinal data also allows for a stronger investigation of an association between changes in sum erosive damage and changes in functional ability, as well as the exploration of factors associated with changes in sum erosive damage that may offer explanations for why some individuals progress, while others remain stable or even improve. Secondly, with impressive reproducibility data already obtained, the next step in the advancement of EERA involves the application of this software in a way that provides insight into clinical questions related to erosive disease [162]–[164]. By pairing EERA with the MRx database and access to participants, it is possible to proceed with a follow-up pilot study.

3.2 Study Objectives

The overarching study objective is to evaluate change in bone erosive damage over time in the MCP 2-5 joints of the worst-affected hand of patients with RA using MRI and EERA. The primary objective is to assess the association between either total change in sum erosive damage or rate of change in sum erosive damage and change in functional ability. The secondary objective is to explore differences in characteristics among study participants who demonstrate improvement in sum erosive damage, study

participants who remain stable and study participants who demonstrate progression, in order to generate possible explanations or concepts related to how erosive damage changes over time.

3.3 Study Questions

3.3.1 Change in Erosive Damage and Functional Ability over Time

When change in RA bone erosions in the MCP 2-5 joints of the worst-affected hand is quantified using MRI and EERA, are total change in sum erosive damage and/or rate of change in sum erosive damage associated with change in functional ability?

3.3.2 Classification of Change in Erosive Damage over Time

When using total change in sum erosive damage as measured by EERA to classify study participants into improvement, stable and progression groups, do any differences in demographic, therapeutic, diagnostic imaging, disease activity and functional ability outcomes emerge that may offer possible explanations for how erosive damage changes over time?

3.4 Study Hypotheses

3.4.1 Change in Erosive Damage and Functional Ability over Time

The null hypothesis is that total change and rate of change in sum erosive damage are not associated with change in functional ability. However, as this is a pilot study, the primary focus related to this study question is to generate data that may provide insight into the relationship between change in sum erosive damage and change in functional ability.

3.4.2 Classification of Change in Erosive Damage over Time

The sole focus of this study question is to generate hypotheses and explore for possible differences among participants that experience improvement in erosive damage, remain stable and progress. Potential concepts or hypotheses that emerge from this study may be further examined in future research.

3.5 Study Participants

3.5.1 Participant Recruitment and Sample Size

Study participants for the initial MRx study were recruited from multiple rheumatology clinics in Hamilton, Ontario, Canada. Recruitment into the MRx study was based on an early referral recommendation for RA that included any of the following criteria: at least three swollen joints, a positive squeeze test for either the MCP or MTP joints or at least 30 minutes of self-reported morning stiffness [180]. As this Master's follow-up project was a pilot study to explore the use of EERA for assessing change in bone erosive damage over time, convenience sampling was used. The inclusion and exclusion criteria implemented for both the MRx study and Master's follow-up study are outlined in the proceeding subsections 3.5.2 and 3.5.3. Forty-three participants were eligible for the follow-up study, with 35 (81.4%) completing the follow-up study visit. Reasons cited by eligible participants who did not engage in the follow-up study included illness and/or lack of availability. A study participant flow diagram is shown in Figure 3.1 and outlines the transition from the baseline study visit, which was conducted as part of the MRx Ph.D dissertation, to the follow-up study visit, which was conducted as part of this M.Sc. dissertation.

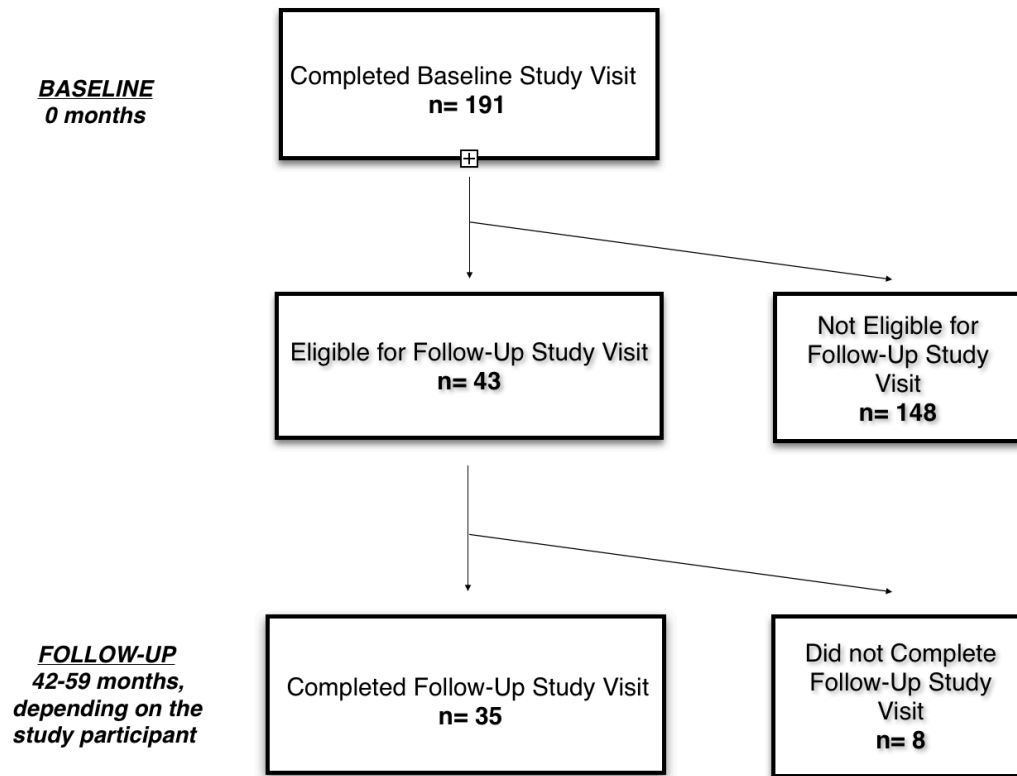


Figure 3.1: Study participant flow diagram outlining the transition from the baseline study visit, which was conducted as part of the MRx Ph.D. dissertation, to the follow-up study visit, which was conducted as part of this M.Sc. dissertation.

3.5.2 Inclusion Criteria

The MRx study used the following inclusion criteria:

- At least 18 years of age at study enrollment
- At least three swollen joints; OR,
- MCP joint(s) positive squeeze test; OR,
- MTP joint(s) positive squeeze test; OR,
- At least 30 minutes of self-reported morning stiffness

- At least six weeks of self-reported symptom duration

For logistical purposes, this follow-up study used the following inclusion criterion:

- Participant belongs to the clinic of Dr. Jonathan D. Adachi, one of the rheumatologist investigators in the MRx study

3.5.3 Exclusion Criteria

The MRx study used the following exclusion criteria:

- Self-reported symptom onset prior to 17 years of age
- History of juvenile arthritis
- Evidence of viral arthritis
- A previously confirmed rheumatologic diagnosis of inflammatory arthritis or conditions that contraindicate treatment with DMARDs, excluding sulfa allergy or medically controlled, non-terminal liver disease
- Patients with psychological deficit or diminished capacity to provide independent, informed consent
- Any contraindication to MRI or X-ray
- Current or planned pregnancy
- Lactating mothers

This follow-up study used the following exclusion criteria:

- Participant was a drop-out in MRx study
- Changes in participant status since the MRx study that would result in exclusion, such as a new contraindication to MRI

3.6 Data Collection

3.6.1 Overview

The follow-up study visits took place approximately 4 years after the baseline visit, with the timespan ranging from 42-59 months depending on the study participant. Upon the participant's arrival at the study location, he/she was greeted and guided through the informed consent process. Given that participant had already engaged in the MRx study, he/she was familiar with the consent process and study visit procedure. The nature of the follow-up study visit and any of the participant's questions or concerns were answered or explained. The informed consent form used at the follow-up study visit can be found in the appendices (Appendix A). Note that the Health Utilities Index Mark 3, which was mentioned in the consent form, was not used in this dissertation.

For data collected at follow-up, the MRx database was accessed to obtain the corresponding baseline data. These data were used for compiling the descriptive statistics of the study population and allowed for an analysis of change over time, as outlined in the study objectives. Table 3.1 illustrates the data items collected over the course of the study duration and specifies whether the data used in this dissertation originated from the baseline visit, follow-up visit or both. The proceeding subsections will provide further details relating to this table. The data collection form used at the follow-up study visit is provided in the appendices (Appendix B). As was the case with the informed consent form, the Health Utilities Index Mark 3 (Section 2.0) was not used in this dissertation. Additionally, patient global health was not used in Section 4.0 related to the DAS28 and

Section 6.0 was used as a general framework for recording prescription information; dose and duration/commencement were not used.

Table 3.1: Data collected at baseline and follow-up study visits, with checkmarks indicating that the data item was collected at the particular visit and used in this dissertation.

Data Item	Baseline	Follow-Up
<i>Demographics:</i> age, gender, dominant hand, ethnic origin, smoking status, symptom onset	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
<i>Medication:</i> First course of DMARDs or biologics initiated more than 12 months prior to baseline study visit	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
<i>Medication:</i> Prescription history of DMARDs, biologics, NSAIDs and corticosteroids during study period	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
<i>Bloodwork:</i> ESR, CRP	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
<i>Swollen and Tender Joint Counts</i>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
<i>MRI of Worst-Affected Hand</i>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
<i>Functional Ability Questionnaire: HAQ-DI</i>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>

CRP: C-reactive protein. DMARD: disease-modifying antirheumatic drug.

ESR: erythrocyte sedimentation rate. HAQ-DI: health assessment questionnaire-disability index.

3.6.2 Demographics

Demographic information for the study population (n=35) was collected during the baseline visit, with age, gender, dominant hand, ethnic origin, smoking status (*“Do you currently or have you ever smoked cigarettes, cigars, or tobacco products?”*) and date of symptom onset (*“When did the patient’s arthritis symptoms first begin, including pain/tenderness, swelling, or stiffness in your joints?”*) obtained.

3.6.3 Medication

At the baseline study visit, medication usage prior to study commencement was addressed in the form of the question, *“Did the patient initiate his/her first course of a DMARD more than 12 months prior to today’s date?”* This question is the only time during this dissertation that the term DMARD also includes biologic agents. Prior to the follow-up study visit, medication history since baseline was evaluated by accessing each participant’s electronic medical record (EMR). Prescription history of DMARDs, biologics, NSAIDs and corticosteroids throughout the study duration was obtained.

3.6.4 Bloodwork

Blood measures from baseline were obtained from the MRx database. Prior to the follow-up study visit, EMR was accessed to obtain serum readings. ESR, rather than CRP, was chosen as the main blood measure for this dissertation, as ESR was the more commonly used measure within the rheumatology clinic. To reduce patient burden, ESR measurements completed either three months before or three months after the follow-up study visit were used. If a participant did not have ESR readings available prior to the

study visit, he/she was provided with a blood requisition to be completed at the laboratory of his/her choice.

3.6.5 Joint Counts

Swollen and tender joint counts were performed at baseline and follow-up by the lead investigator of the Ph.D. and M.Sc. dissertation, respectively. The modified standard operating procedure can be found in the appendices (Appendix C), as well as the homunculi used for recording the data (Appendices D and E).

3.6.6 Magnetic Resonance Imaging Protocol

Study participants had an MRI scan of their worst-affected hand performed at baseline and follow-up study visits, with the worst-affected hand determined at baseline using cumulative tender and swollen joint counts. A 1.0T OrthOne pMRI scanner (General Electric Healthcare, Wilmington, MA) was used for the study. Prior to the study visit, a daily quality assurance test was performed to ensure proper functioning of the scanner. During the study visit, each participant completed an MRI safety form (Appendix F) and was asked to remove any keys, watches or hand jewelry. The participant was then seated in an inclined chair inside of the MRI room. A large pillow was placed behind the participant's head for support. The participant was given a padded wrist guard and their hand was inserted inside the coil. The participant's outstretched arm and shoulder were supported with pillows and a mobile ottoman. A 100mm diameter coil was used for the majority of participants, while a 110mm coil was used for participants with very large hands. Once the hand was in place, small cushions were inserted inside the coil to provide further stability. To maximize comfort, the participant was frequently

asked if any adjustments to the chair, ottoman, arm or hand positioning were desired. Once the general positioning of the hand was deemed satisfactory and the participant affirmed that he/she was comfortable, a localizer test to confirm proper positioning using sagittal, axial and coronal scout scans was conducted. If necessary, further adjustments to hand positioning were made based on the images obtained from the localization process. Next, a gradient shim test was performed to assess for possible imaging interference. If interference was detected, the frame of the MRI-room door was wiped down to remove any dust or residue. Lastly, centre frequencies were aligned using a plot scale. After completion of these tests, the protocol was initiated.

The MRI protocol used during the MRx study consisted of six sequences, which are listed below:

1. FSE T1w Axial Scout (4 slices)
2. 3DGE –FS Coronal (32 slices; 40 slices if hand was large)
3. 3DGE –FS Coronal (32 slices; 40 slices if hand was large)
4. FSE STIR Coronal (16 slices)
5. FSE T2w +FS Axial (18 slices)
6. FSE T1w –FS Axial (16 slices)

While the same protocol was performed at the follow-up study visit, only the second sequence was used for data analysis in this follow-up study based on EERA specifications. The parameters for this sequence are outlined in Table 3.2.

Table 3.2: MRI parameters for the 3DGE –FS coronal sequence used for EERA analysis.

Sequence Type	3-D Gradient Echo
Fat Saturation	No
Orientation	Coronal
Number of Excitations	1
Repetition Time	60 ms
Echo Time	6.6 ms
Bandwidth	50 kHz
Flip Angle	60°
Field of View	140 x 140 mm
Imaging Matrix	512 x 256 (resampled to 512 x 512)
Number of Slices	32 (40 for larger hands)
Slice Thickness	1 mm
Interslice Gap	0 mm
Voxel Dimensions	0.273 x 0.273 x 1.000 mm
Inversion Recovery	No

In total, the MRI protocol took approximately 30-40 minutes to complete from start to finish, with 5 to 10 minutes of participant positioning adjustments and computer preparation and 25 to 30 minutes of scanning. On completion of the scanning procedure, images were archived and the participant was ushered from the MRI-room.

3.6.7 Health Assessment Questionnaire- Disability Index

The HAQ-DI was administered to participants during both baseline and follow-up visits [113]–[115]. Participants had the option of either completing the questionnaire at the end of the study visit or completing it at home and mailing it back to the rheumatology clinic within a time frame of two months. If a participant was not comfortable completing the questionnaire independently (e.g. vision problems, language barrier, difficulties with comprehension, etc), the questions were read aloud and any concerns were addressed. The questionnaire can be found on the Stanford University website at <http://aramis.stanford.edu/downloads/HAQ%20-%20DI%202007.pdf> and is included in the appendices (Appendix G). Please note that page 3 of the questionnaire, which contains an additional question about activities, as well as a pain and overall health assessment, is not used in the scoring of the disability index and thus was not included in the appendices. Scoring of the HAQ-DI is discussed in Section 3.7.4.

The HAQ-DI assesses functional ability under eight categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip and activities. Each item contains a set of 2-3 questions that can be responded to using one of four options: 0 (without any difficulty), 1 (with some difficulty), 2 (with much difficulty) and 3 (unable to do). All items, with the exception of “activities,” also include a section focusing on aides and devices used to complete certain tasks. For example, use of specialized eating utensils is taken into account for the “eating” item. Respondents also have the opportunity to indicate if they require assistance from another person for any of the eight items.

3.7 Data Analyses

3.7.1 Baseline Rheumatoid Arthritis Magnetic Resonance Imaging Score

Four radiologists from McMaster University and Hamilton Health Sciences in Hamilton, Ontario, Canada participated in the original MRx study. While the radiologists were not involved in the follow-up study visit, they did evaluate MR images using RAMRIS at baseline. The RAMRIS form used by the radiologists to score images is provided in the appendices (Appendix H). Not all radiologists evaluated every baseline image. Therefore, in an attempt to ensure as much consistency as possible, the radiologist who scored the most baseline images belonging to follow-up participants was chosen as the main assessor. The main radiologist's scores were used whenever possible. If the main radiologist did not evaluate an image, the radiologist who was next in line in terms of number of images scored was chosen. Of the 35 RAMRIS scores obtained, 31 (88.6%) were completed by the main radiologist, 3 (8.6%) by a second radiologist and 1 (2.8%) by a third radiologist.

3.7.2 Disease Activity Score with 28-Joint Count

The three-version DAS28-ESR was used in this study and consists of three components: swollen joint counts, tender joint counts and ESR [106]. An online DAS28 calculator created by the developers of the DAS28 at Radboud University in Nijmegen, Netherlands was used to calculate the DAS28 at baseline and follow-up and can be found at <http://www.das-score.nl/das28/DAScalculators/dasculators.html>.

3.7.3 Early Erosions in Rheumatoid Arthritis Segmentation

EERA was used to evaluate baseline and follow-up MR images for erosive damage. Prior to analysis, the lead investigator of the current study, MT, completed a training session led by an undergraduate student, MJ, most familiar with the software. This training session included both guided and independent practice using approximately 10 images to learn the software basics, with each image capturing the MCP 2-5 joints of either a right or left hand. The high reproducibility of EERA has already been reported and was not the focus of this thesis [162]–[164]. However, to ensure that MT was adequately trained in use of the software and could perform EERA analysis reliably, another set of images were analyzed in order to determine MT's inter- and intra-rater reliability. The sample size of the images evaluated was determined based on ICCs from past trainees, where the use of approximately 10 images resulted in a lower-bound confidence interval (CI) of roughly 0.80. Given that ICCs ≥ 0.80 are indicative of excellent reliability, a sample size of 10 or above was deemed acceptable. Ultimately, another 19 images that MJ had also used during his EERA training were analyzed by MT for this reliability training exercise. The methodology and analyses used for this evaluation were based on a recently accepted manuscript by Tomizza *et al.* [164]. Twenty-one erosions were found within the 19 images; MT calculated the sum erosive damage for each image and then repeated the segmentations one week after initial readings. MT was blinded to his initial readings when repeating the analyses and was also blinded to the scores of MJ during both readings. Two-way mixed effects models with absolute agreement single measures and average measures ICCs (95% CIs) were used to

assess inter- and intra-rater reliability [165]. To determine inter-rater reliability, MT's initial readings were compared to the scores of MJ. To determine intra-rater reliability, MT's initial readings were compared to his second readings taken one week later. Tomizza *et al.* found that when evaluating the reliability of EERA, performing a log-transformation of sum erosive damage was beneficial in terms of satisfying ICC assumptions related to variance [164], [181]. Therefore, for this reliability training exercise, sum erosive damage scores were log-transformed. Given that reliability of EERA is associated with study methodology and is not one of the study objectives, the reliability findings are presented here in Table 3.3. ICCs above 0.8 indicate excellent agreement, which are seen for both inter- and intra-rater reliability.

Table 3.3: Intra-class correlation coefficients assessing the inter- and intra-rater reliability of EERA analysis performed by MT.

Raters	Single Measures ICC (95% Confidence Intervals)	Average Measures ICC (95% Confidence Intervals)
<i>MT + MJ</i> <i>Inter-rater reliability for MT</i>	0.867 (0.686 to 0.947)	0.929 (0.814 to 0.973)
<i>MT Run 1 + MT Run 2</i> <i>Intra-rater reliability for MT</i>	0.910 (0.783 to 0.964)	0.956 (0.878 to 0.982)

MT performed all EERA analyses for follow-up images, while MJ had previously analyzed the majority of baseline images. If MT found that a participant's baseline images had not been evaluated using EERA, he performed this analysis. The protocol for EERA segmentation was outlined in the Section 2.4.4. After segmentation, the total erosive damage for each MR image was summed. For example, if two erosions were found on MCP2 and MCP3, these volume scores were added to create a total sum damage score in (mm³). For each participant, the sum damage score at baseline was subtracted from the sum damage score at follow-up to determine the total change in sum erosive damage. Negative change scores indicate that sum erosive damage decreased and represent improvement, while positive change scores indicate that sum erosive damage increased and represent progression. Rate of change in sum erosive damage was also

calculated by dividing the total change score by the amount of time between baseline and follow-up visits in months. A multiplication factor of 12 was subsequently applied to produce a final rate of change in sum erosive damage score (mm^3/year). The number of erosions found for each participant, as well as the location of the erosion (e.g. MCP2), was also recorded.

3.7.4 Health Assessment Questionnaire- Disability Index

The HAQ-DI was used as a measure of functional ability [113]–[115]. Scoring instructions were obtained from the National Institutes of Health and can be found online at https://www.niehs.nih.gov/research/resources/assets/docs/haq_instructions.pdf. Each of the eight items was assigned a component score from 0 to 3, based on the highest score for any of the questions found in the specified category. Additionally, if respondents indicated that an aid/device or assistance was required within that category, the minimum score was raised to 2. For example, if the highest score for any of the questions in the “eating” section was 1, but the respondent indicated that he/she used a specialized eating utensil, then the score for that section was raised to 2. However, if the score was already 2 or 3 prior to taking into account aids/devices or assistance, no changes were made. After completing this process for each item, the 8 subscores were summed and the average was taken to produce a final HAQ-DI score ranging from 0 to 3. This process was completed for both baseline and follow-up study visits and a change score was calculated by subtracting the baseline HAQ-DI from the follow-up HAQ-DI, with negative change scores indicating improvement in functional ability and positive change scores indicating worsening.

3.7.5 Statistical Analyses: Change in Erosive Damage and Functional Ability over Time

Statistical analyses were performed using SPSS Statistics version 22 (IBM, NY). Descriptive statistics were determined for the sample population (n=35) using baseline data and follow-up data. The nonparametric Spearman's rho (r_s) was used to examine the correlation between a) total change in sum erosive damage and change in HAQ-DI and b) rate of change in sum erosive damage and change in HAQ-DI. Two participants did not complete the HAQ-DI at follow-up and were not included in either of the correlation models.

3.7.6 Exploratory Analyses: Classification of Change in Erosive Damage over Time

Participants were classified into one of three groups based on total change in sum erosive damage from baseline to follow-up: improvement (decrease $> 17.1 \text{ mm}^3$), stable (decrease $\leq 17.1 \text{ mm}^3$ or increase $\leq 17.1 \text{ mm}^3$) and progression (increase $> 17.1 \text{ mm}^3$). These thresholds were based on smallest detectable difference calculations outlined in a conference abstract [163]. Point-in-time and change-over-time measures in inter- and intra-rater scenarios were evaluated, as outlined in Table 3.4.

Table 3.4: Smallest detectable difference values for point-in-time/change-over-time and inter/intra-rater measures using EERA.

Scenario	Smallest Detectable Difference
<u>Point-in-Time: Inter-rater</u>	<i>All image sets (n=92) → 59.7 mm³</i> <i>Image sets with mean total erosion volume < 100 mm³ (n=70) → 11.8 mm³</i>
<u>Point-in-Time: Intra-rater</u>	<i>All image sets (n=92) → 31.1 mm³</i> <i>Image sets with mean total erosion volume < 100 mm³ (n=70) → 5.5 mm³</i>
<u>Change-over-Time: Inter-rater</u>	<i>All image sets (n=24) → 74.0 mm³</i> <i>Image sets with mean total erosion volume < 100 mm³ (n=18) → 17.1 mm³</i>
<u>Change-over-Time: Intra-rater</u>	<i>All image sets (n=24) → 34.4 mm³</i> <i>Image sets with mean total erosion volume < 100 mm³ (n=18) → 9.3 mm³</i>

Given that this dissertation investigated change over time and involved two raters (MJ at baseline and MT at follow-up), the change-over-time/inter-rater SDD was deemed as the most applicable to this study. With 32 out of 35 participants (91.4%) having less than 100mm³ of sum erosive damage at baseline and 31 (88.6%) having less than 100 mm³ of sum erosive damage at follow-up, 17.1 mm³ was selected as the most appropriate threshold for determining true change. Thus, participants with total changes less than 17.1 mm³ in either direction were classified under the “stable” group. Tables outlining various demographic, therapeutic, diagnostic imaging, disease activity and functional ability outcomes were created to allow for visual examination of possible differences among the

three groups, with the ultimate goal of identifying potential concepts or hypotheses related to how erosive damage changes over time.

Chapter Four: Results

4.1 Descriptive Statistics

The median (interquartile range, IQR, presented as “quartile 1, quartile 3”) timespan between baseline and follow-up study visits for this study population of RA patients (n=35) was 4.4 (4.3, 4.6) years, with 22 participants (63%) having their right-hand scanned. Demographic data, including age, gender, dominant hand, ethnic origin, smoking status and symptom onset, is outlined in Table 4.1. Table 4.2 provides the medication data for this sample population from baseline to follow-up, as well as initiation of DMARDs or biologics more than 12 months prior to the baseline visit. Of the 4 medication classes assessed from baseline to follow-up, the following drugs were prescribed: DMARDs (MTX, leflunomide, sulfasalazine and hydrochloroquine), biologics (abatacept, adalimumab, certolizumab pegol, etanercept, rituximab and tocilizumab), NSAIDs (celecoxib, diclofenac and naproxen) and corticosteroids (prednisone). Diagnostic imaging measures, consisting of RAMRIS scores (baseline) and EERA assessments (baseline and follow-up), are presented in Tables 4.3, 4.4 and 4.5. Tables 4.6 and 4.7 focus on disease activity measures, with joint counts, ESR, CRP and DAS28 values provided for both baseline and follow-up study visits. Lastly, functional ability at baseline and follow-up, as well as change in functional ability, are illustrated via boxplots in Figures 4.1, 4.2 and 4.3.

Table 4.1: Demographic data for study population (n=35).

DEMOGRAPHIC VARIABLE	STUDY POPULATION (n=35)
<u>Age (years)</u> [median (IQR)]	58 (47, 63)
<i>Minimum:</i>	35
<i>Maximum:</i>	77
<u>Gender</u> (n, % female)	27, 77.1%
<u>Dominant Hand</u> (n, % right-handed)	32, 91.4%
<u>Ethnic Origin</u>	
<i>White/Caucasian</i> (n, %)	29, 82.8%
<i>Black</i> (n, %)	2, 5.7%
<i>South Asian</i> (n, %)	2, 5.7%
<i>Latin American</i> (n, %)	1, 2.9%
<i>Other</i> (n, %)	1, 2.9%
<u>Smoking Status</u>	
<i>Yes</i> (n, %)	15, 42.9%
<i>No</i> (n, %)	16, 45.7%
<i>Missing Data</i> (n, %)	4, 11.4%
<u>Symptom Onset (years)</u> [median (IQR)]	4.8 (2.0, 9.5)
<i>Minimum:</i>	0.5
<i>Maximum:</i>	25.6

Table 4.2: Medication data for study population (n=35).

MEDICATION VARIABLE	STUDY POPULATION (N=35)
	<i>Yes (n, %)</i>
<u>First Course of a DMARD or Biologic Initiated >12 Months Prior to Baseline</u>	18, 51.4%
<u>Use of DMARDs During Study Period*</u>	28, 80%
<u>Use of Biologics During Study Period*</u>	21, 60%
<u>Use of Both DMARDs and Biologics During Study Period* **</u>	15, 42.9%
<u>Use of NSAIDs During Study Period*</u>	12, 34.4%
<u>Use of Corticosteroids During Study Period *</u>	9, 25.7%

DMARD: disease-modifying antirheumatic drug. NSAID: non-steroidal anti-inflammatory drug.

** Medication usage information based on prescription history log in electronic medical record.*

*** “Use of both DMARDs and biologics” represents prescriptions of both medications at any point in the study period and does not necessarily imply simultaneous use.*

Table 4.3: Diagnostic imaging measures (part 1 of 3: baseline RAMRIS scores) for the study population (n=35).

DIAGNOSTIC IMAGING VARIABLE	STUDY POPULATION (n=35)	MIN.	MAX.
<u>Baseline RAMRIS Synovitis Score*</u> [median (IQR)]	2.0 (0.0, 4.0)	0	10
<u>Baseline RAMRIS Bone Marrow Edema Score*</u> [median (IQR)]	1.0 (0.0, 2.0)	0	11
<u>Baseline RAMRIS Bone Erosion Score*</u> [median (IQR)]	4.0 (2.0, 8.0)	0	35
<u>Baseline Total RAMRIS Score*</u> [median (IQR)]	7.0 (2.0, 15.0)	0	56

RAMRIS: rheumatoid arthritis magnetic resonance imaging scoring system.

** RAMRIS scores calculated for the single hand imaged for this study.*

Table 4.4: Diagnostic imaging measures (part 2 of 3: baseline EERA) for the study population (n=35).

DIAGNOSTIC IMAGING VARIABLE	STUDY POPULATION (n=35)
Baseline EERA Sum Erosive Damage* (mm^3) [median (IQR)]	12.6 (0.0, 39.7)
Minimum:	0.0
Maximum:	702.7
Baseline EERA Number of Erosions*	0.9 (0.8)
Participants with 0 erosions (n, %)	11, 31.4%
Participants with 1 erosion (n, %)	18, 51.4%
Participants with 2 erosions (n, %)	4, 11.4%
Participants with 3 erosions (n, %)	2, 5.8%
Baseline EERA Location of Erosions* **	
MCP2 (n, % of total erosions)***	10, 31.3%
MCP3 (n, % of total erosions)	13, 40.6%
MCP4 (n, % of total erosions)	5, 15.6%
MCP5 (n, % of total erosions)	4, 12.5%

EERA: early erosions in rheumatoid arthritis.

* *EERA analyses represent erosive damage of the single hand imaged for this study.*

** *Erosion(s) may be located on right or left MCPs, depending on the hand imaged.*

*** *One of these erosions was found on the proximal phalange of the MCP joint, rather than the head of the metacarpal.*

Table 4.5: Diagnostic imaging measures (part 3 of 3: follow-up EERA) for the study population (n=35).

DIAGNOSTIC IMAGING VARIABLE	STUDY POPULATION (n=35)
Follow-Up EERA Sum Erosive Damage* (mm^3) [median (IQR)]	14.2 (0.0, 29.3)
Minimum:	0.0
Maximum:	401.3
Follow-Up EERA Number of Erosions*	0.9 (0.8)
Participants with 0 erosions (n, %)	10, 28.6%
Participants with 1 erosion (n, %)	19, 54.3%
Participants with 2 erosions (n, %)	4, 11.4%
Participants with 3 erosions (n, %)	2, 5.7%
Follow-Up Location of Erosions* **	
MCP2 (n, % of total erosions) ***	10, 30.3%
MCP3 (n, % of total erosions)	13, 39.4%
MCP4 (n, % of total erosions)	6, 18.2%
MCP5 (n, % of total erosions)	4, 12.1%

EERA: early erosions in rheumatoid arthritis.

* *EERA analyses represent erosive damage of the single hand imaged for this study.*

** *Erosion(s) may be located on right or left MCPs, depending on the hand scanned.*

*** *One of these erosions was found on the proximal phalange of the MCP joint, rather than the head of the metacarpal.*

Table 4.6: Baseline disease activity measures for the study population (n=35).

DISEASE ACTIVITY VARIABLE	STUDY POPULATION (n=35)	MIN.	MAX.
<u>Baseline Swollen Joint Count</u> (n) [median (IQR)]	12.0 (7.8, 14.3)	0	22
<u>Baseline Tender Joint Count</u> (n) [median (IQR)]	4.5 (1.5, 13.5)	0	24
<u>Baseline ESR</u> (mm/hr) [median (IQR)]	14.0 (9.0, 26.0)	1	60
<u>Baseline CRP</u> (mg/L) [median (IQR)]	4.0 (1.1 10.7)	0	91
<u>Baseline DAS28*</u> [median (IQR)]	4.5 (3.4, 5.7)	2.1	6.9

CRP: c-reactive protein. DAS28: disease activity score with 28-joint count.

ESR: erythrocyte sedimentation rate.

** 3-variable DAS28 used, consisting of swollen joint counts, tender joint counts and ESR.*

Table 4.7: Follow-up disease activity measures for the study population (n=35).

DISEASE ACTIVITY VARIABLE	STUDY POPULATION (n=35)	MIN.	MAX.
<u>Follow-Up Swollen Joint Count (n)</u> [median (IQR)]	3.0 (0.0, 6.0)	0	17
<u>Follow-Up Tender Joint Count (n)</u> [median (IQR)]	3.0 (0.0, 6.0)	0	27
<u>Follow-Up ESR (mm/hr)</u> [median (IQR)]	8.0 (4.0, 13.8)	2	31
<u>Follow-Up CRP (mg/L)</u> [median (IQR)]	Not enough data	Not enough data	Not enough data
<u>Follow-Up DAS28*</u> [median (IQR)]	3.1 (2.2, 4.0)	0.7	5.7
<u>Change in DAS28*</u> [median (IQR)]	- 1.6 (-2.5, -0.6)	- 4.6	1.7

CRP: c-reactive protein. DAS28: disease activity score with 28-joint count.

ESR: erythrocyte sedimentation rate.

** 3-variable DAS28 used, consisting of swollen joint counts, tender joint counts and ESR.*

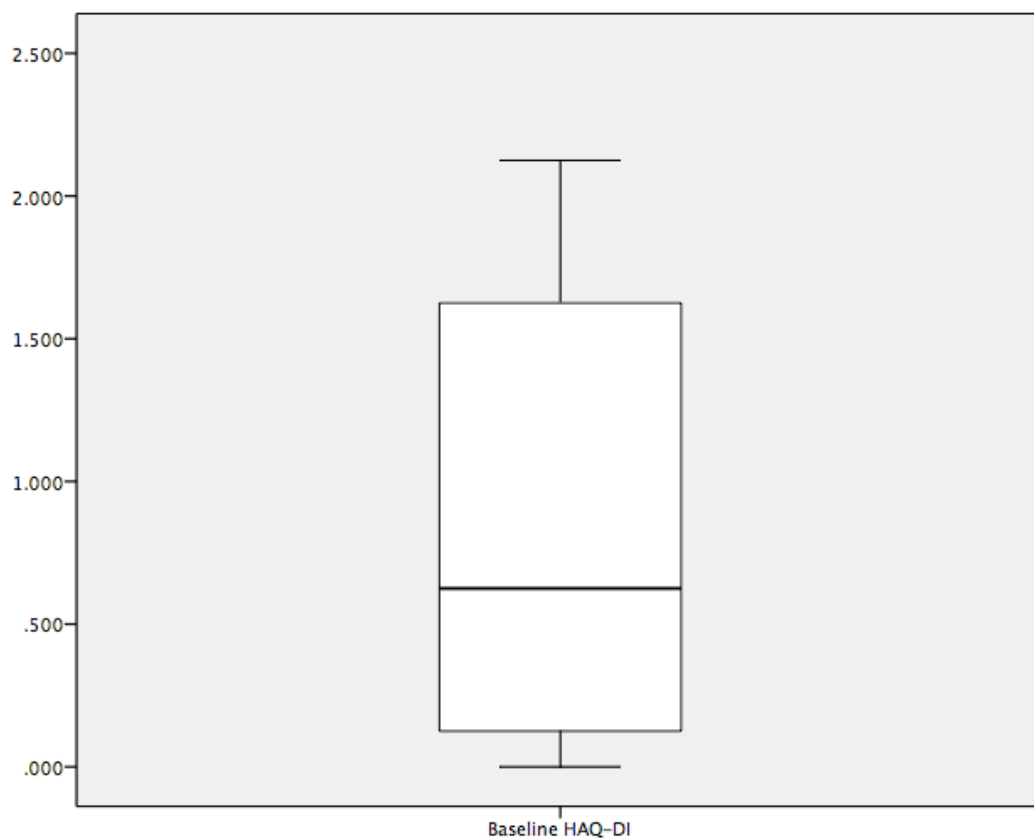


Figure 4.1: Boxplot of HAQ-DI values at the baseline study visit, with the top and bottom ends of the box representing the 3rd and 1st quartiles, respectively, the horizontal line inside of the box representing the median and the whiskers representing the most extreme values that are not outliers.

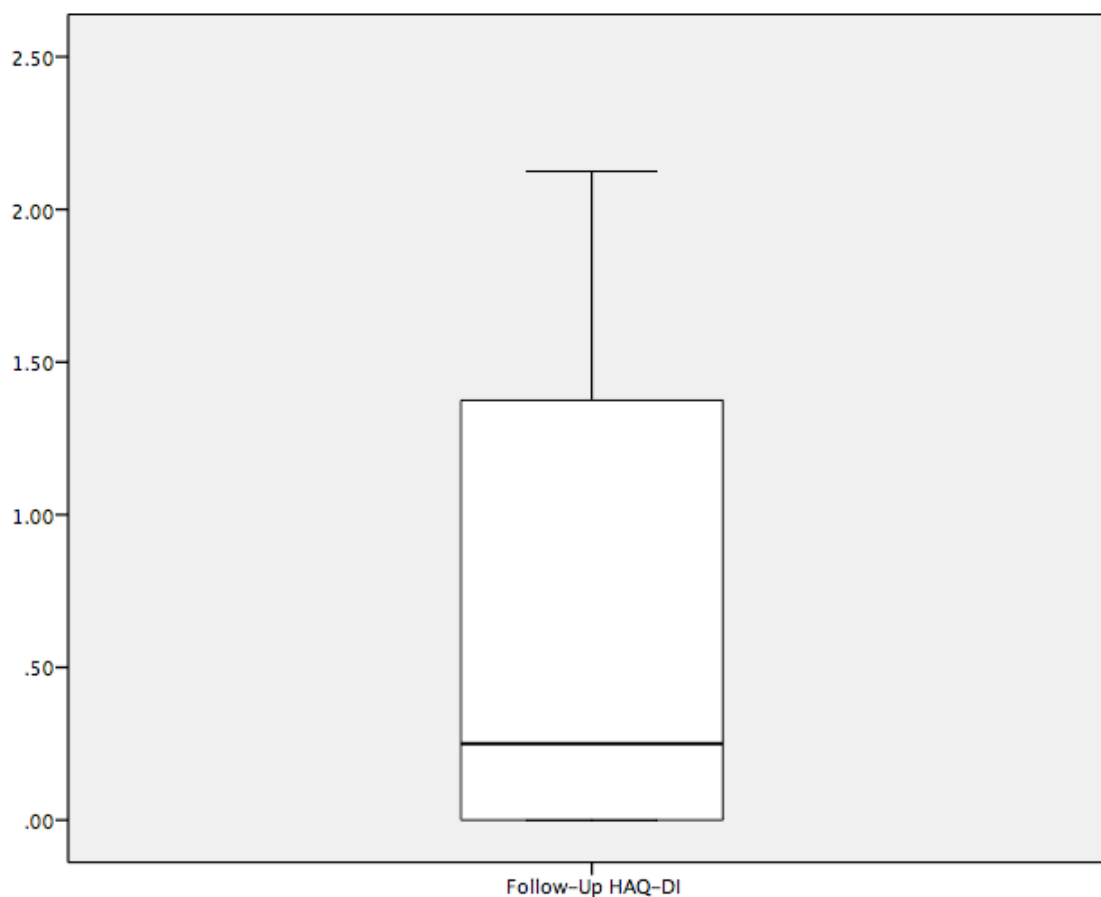


Figure 4.2: Boxplot of HAQ-DI values at the follow-up study visit, with the top and bottom ends of the box representing the 3rd and 1st quartiles, respectively, the horizontal line inside of the box representing the median and the whiskers representing the most extreme values that are not outliers.

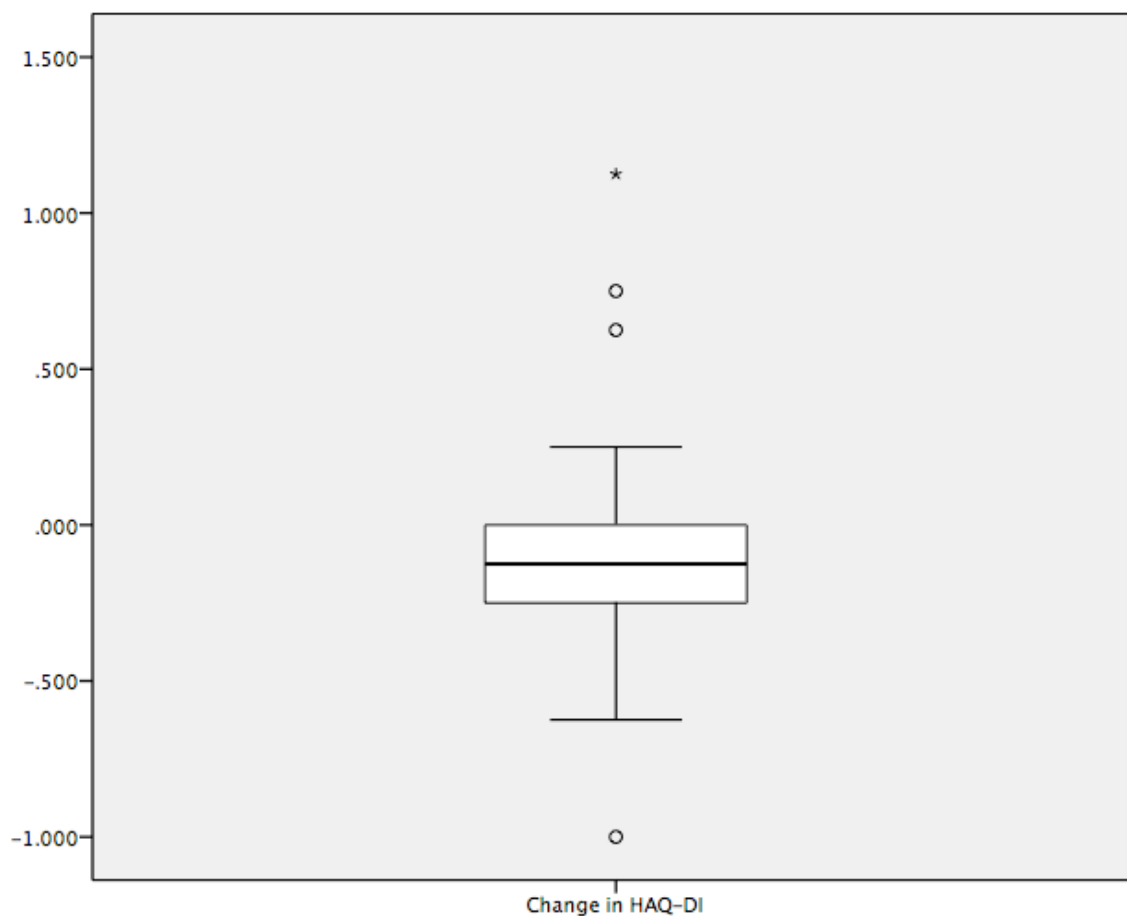


Figure 4.3: Boxplot of change in HAQ-DI values from baseline to follow-up study visits, with the top and bottom lines of the box representing the 3rd and 1st quartiles, respectively, the horizontal line inside of the box representing the median and the whiskers representing the most extreme values that are not outliers. In this figure, the circles and the asterisk beyond the whiskers represent outliers.

4.2 Change in Erosive Damage and Functional Ability over Time

Spearman's rho (r_s) was used in this dissertation. Two of the 35 study participants (5.7%) did not have HAQ-DI scores available at follow-up and were excluded from both models. Firstly, r_s was used to assess the relationship between total change in sum erosive damage and change in functional ability, as measured by the HAQ-DI. The median (IQR) total change in sum erosive damage over time for all 35 study participants was 0.0 (-1.2, 8.6) mm³, with minimum of -301.4 mm³ and a maximum of 73.7 mm³. After removing the two participants not included in the analyses, the median (IQR) total change in sum erosive damage became 0.1 (-3.1, 9.2) mm³. The median (IQR) change in HAQ-DI was -0.1 (-0.3, 0.1), with a minimum of -1.0 and a maximum of 1.1. The r_s (p-value) was 0.099 (0.585).

Secondly, r_s was used evaluate the relationship between rate of change in sum erosive damage and change in functional ability. The median (IQR) rate of change in sum erosive damage for all 35 study participants was 0.0 (-0.2, 1.9) mm³/year, with a minimum of -70.9 mm³/year and a maximum of 19.7 mm³/year. After removing the two participants not included in the analyses, the median (IQR) remained 0.0 (-0.7, 2.1) mm³/year. The r_s (p-value) was 0.104 (0.565).

4.3 Classification of Change in Erosive Damage over Time

Total change in sum erosive damage was used to classify study participants into three groups: improvement, stable and progression. Five study participants (14.3%) demonstrated improvement, 27 (77.1%) remained stable and 3 (8.6%) demonstrated

progression. The following tables outline various demographic, therapeutic, diagnostic imaging, disease activity and functional ability measures and allow for visual inspection of possible differences among the three groups. Table 4.8 assesses demographic characteristics, while Table 4.9 examines medication variables. Tables 4.10 and 4.11 outline diagnostic imaging measures. Lastly, Table 4.12 provides an outlook on disease activity and functional ability. Note that mean (standard deviation, SD) is used in this exploratory analysis, rather than median (IQR).

Table 4.8 A comparison of the baseline demographic data of study participants based on total change in sum erosive damage from baseline to follow-up.

<i>Characteristic</i>	<i>Change in Sum Erosion Damage</i>		
	Improvement	Stable	Progression
	<i>n= 5</i>	<i>n= 27</i>	<i>n= 3</i>
<u>Age</u> (years) [mean (SD)]	57.6 (8.0)	54.7 (12.0)	60.7 (4.9)
<u>Gender</u> (% female)	40.0%	85.2%	66.7%
<u>Ethnic Origin</u> (% white/Caucasian)	60.0%	85.2%	100.0%
<u>Smoking Status</u> (% yes)	80.0%	51.9%	66.7%
<u>Symptom Onset</u> (years) [mean (SD)]	5.6 (5.1)	6.7 (6.1)	4.4 (3.6)

Table 4.9: A comparison of the medication data of study participants throughout the study period based on total change in sum erosive damage from baseline to follow-up.

<i>Characteristic</i>	<i>Change in Sum Erosion Damage</i>		
	Improvement	Stable	Progression
	<i>n= 5</i>	<i>n= 27</i>	<i>n= 3</i>
<u>First Course of DMARDs or Biologics Initiated > 12 Months Prior to Baseline (% yes)</u>	80.0%	44.5%	66.7%
<u>Use of DMARDs During Study Period* (% yes)</u>	80.0%	60.0%	100%
<u>Use of Biologics During Study Period* (% yes)</u>	20.0%	51.4%	66.7%
<u>Use of Both DMARDs and Biologics During Study Period** (% yes)</u>	0.0%	37.1%	66.7%
<u>Use of NSAIDs During Study Period* (% yes)</u>	20.0%	20.0%	33.3%
<u>Use of Corticosteroids During Study Period* (% yes)</u>	20.0%	28.6%	33.3%

DMARD: disease-modifying antirheumatic drug. NSAID: non-steroidal anti-inflammatory drug.

** Medication usage information based on prescription history log in electronic medical record.*

*** “Use of both DMARDs and biologics” represents prescriptions of both medications at any point in the study period and does not necessarily imply simultaneous use.*

Table 4.10: A comparison of the baseline diagnostic imaging measures (part 1 of 2: baseline RAMRIS) of study participants based on total change in sum erosive damage from baseline to follow-up.

<i>Characteristic</i>	<i>Change in Sum Erosion Damage</i>		
	Improvement	Stable	Progression
	<i>n= 5</i>	<i>n= 27</i>	<i>n= 3</i>
<u>Baseline RAMRIS Synovitis Score*</u> [mean (SD)]	4.8 (4.6)	2.2 (1.9)	0.7 (1.2)
<u>Baseline RAMRIS Bone Marrow Edema Score*</u> [mean (SD)]	4.8 (3.9)	1.6 (2.2)	0.7 (0.6)
<u>Baseline RAMRIS Bone Erosion Score*</u> [mean (SD)]	14.2 (12.5)	3.9 (3.4)	5.7 (3.8)
<u>Baseline Total RAMRIS Score*</u> [mean (SD)]	24.4 (20.3)	7.4 (6.3)	7.0 (5.3)

RAMRIS: rheumatoid arthritis magnetic resonance imaging scoring system.

** RAMRIS scores calculated for the single hand imaged in this study.*

Table 4.11: A comparison of the baseline diagnostic imaging measures (part 2 of 2: baseline EERA) of study participants based on total change in sum erosive damage from baseline to follow-up.

<i>Characteristic</i>	<i>Change in Sum Erosion Damage</i>		
	Improvement	Stable	Progression
	<i>n= 5</i>	<i>n= 27</i>	<i>n= 3</i>
<u>Baseline EERA Sum Erosive Damage*</u> (mm^3) [mean (SD)]	233.6 (265.1)	14.5 (27.3)	45.1 (11.7)
<u>Baseline EERA Number of Erosions*</u> [mean (SD)]	1.4 (0.9)	0.7 (0.7)	2.0 (1.0)
<u>Baseline EERA Location of Erosions* **</u>	MCP2	MCP3	MCP3

EERA: early erosions in rheumatoid arthritis.

** EERA analysis represents erosive damage of the single hand imaged in this study.*

*** Most common site of erosion for each group.*

Table 4.12: A comparison of the baseline disease activity and functional ability of study participants based on total change in sum erosive damage from baseline to follow-up.

<i>Characteristic</i>	<i>Change in Sum Erosion Damage</i>		
	Improvement	Stable	Progression
	<i>n</i> = 5	<i>n</i> = 27	<i>n</i> = 3
<u>Baseline Swollen Joint Count</u> (<i>n</i>) [mean (SD)]	11.2 (7.5)	11.3 (5.7)	11.7 (2.5)
<u>Baseline Tender Joint Count</u> (<i>n</i>) [mean (SD)]	1.2 (1.8)	10.2 (8.4)	4.3 (7.5)
<u>Baseline ESR</u> (mm/hr) [mean (SD)]	11.0 (3.2)	20.3 (15.1)	20.0 (7.2)
<u>Baseline CRP</u> (mg/L) [mean (SD)]	2.9 (2.6)	11.9 (19.0)	6.5 (7.1)
<u>Baseline DAS28*</u> [mean (SD)]	3.3 (0.9)	4.8 (1.7)	4.1 (1.5)
<u>Baseline HAQ-DI</u> [mean (SD)]	0.1 (0.2)	0.9 (0.8)	0.7 (1.0)

CRP: c-reactive protein. DAS28: disease activity score with 28-joint count.

ESR: erythrocyte sedimentation rate. HAQ-DI: health assessment questionnaire-disability index.

** 3-variable DAS28 used, consisting of swollen joint counts, tender joint counts and ESR.*

Chapter Five: Discussion

In this pilot study, a longitudinal evaluation of MCP 2-5 bone erosions in the worst-affected hand of patients with RA was conducted using MRI and EERA software. This study set out to address two main objectives. Firstly, r_s was used to investigate the relationship between *a)* change in total sum erosive damage and change in functional ability and *b)* rate of change in sum erosive damage and change in functional ability. Secondly, participants were classified into three groups based on their total change in sum erosive damage: improvement, stable and progression. Various demographic, therapeutic, diagnostic imaging, disease activity and functional ability outcomes were examined among the three groups using an exploratory, non-statistical approach in order to generate ideas and concepts that may warrant further investigation in future studies. This is the first study to investigate the relationship between either total change or rate of change in sum erosive damage and change in functional ability using EERA. Additionally, this is the first study to classify RA patients under three groups based on change in EERA sum erosive damage scores for the purposes of examining possible differences among the three groups. Ultimately, this study is an important step in the advancement of EERA for use in both the research and clinical settings.

5.1 Change in Erosive Damage and Functional Ability over Time

Total change and rate of change in sum erosive damage were both calculated in this study as measures of erosive damage over time. Each approach has its strengths and

weaknesses. Total change provides a more straightforward interpretation and is used in the majority of studies found in the literature. However, given that the study window varied from 42 to 59 months for participants in this pilot study, depending on the date of their baseline and follow-up visits, some individuals had more time to experience change in erosive damage than others. Rate of change addresses this concern by adjusting for discrepancies in the timing of study visits, but is limited by a slightly more complex interpretation and is not commonly used in the literature. For all 35 study participants, the median (IQR) total change in sum erosive damage over time was 0.0 (-1.2, 8.6) mm³ and the median (IQR) rate of change in sum erosive damage was also 0.0 (-0.2, 1.9) mm³/year. Overall, these values indicate very little change in erosive damage over time within this sample population. In terms of functional ability, the median (IQR) baseline HAQ-DI was 0.6 (0.1, 1.6) and is similar to baseline scores reported in other studies assessing change in functional ability in RA patients [182]. Scores between 0 and 1 are interpreted as mild to moderate disability, indicating that, on average, this group of patients did not experience severe functional limitations at study initiation [114]. HAQ-DI scores slightly improved over time, with median (IQR) follow-up scores of 0.3 (0.0, 1.4).

Two Spearman correlation coefficients were obtained to assess the association between either total change in sum erosive damage or rate of change in sum erosive damage and change in functional ability. The null hypothesis was that neither measure of erosive damage over time was associated with change in functional ability. Considering that this is a pilot study, emphasis should be placed on determining clinical significance via interpretation of the correlation coefficient, rather than statistical significance via

interpretation of the p-value. However, it is worth noting that both p-values were >0.500 , meaning that any associations reflected by the correlation coefficients are not significantly different than no association at all. Starting with total change in sum erosive damage, the correlation coefficient was 0.099, which indicates a very weak association with change in functional ability. Similarly, rate of change in sum erosive damage had a correlation coefficient of 0.104, which also reflects a very weak association with change in functional ability. Collectively, the null hypothesis that total change in sum erosive damage and rate of change in sum erosive damage are not associated with change in functional ability cannot be rejected based on the results of this pilot study.

The relationship between erosive damage and functional ability is complex, with a variety of findings reported in the literature. Two longitudinal studies with a timespan of 3 years found a statistically significant association between radiographic damage and functional ability in patients with early RA [183], [184]. However, this pilot study is in agreement with another two longitudinal studies ranging from 5 to 10 years in length that found no association between functional ability and radiographic damage in patients with early RA [172], [185]. Two possible explanations may clarify the lack of a strong association found in this pilot study. The first argument relates to medication usage. Courvoisier *et al.* suggested that the lack of an association between radiographic damage and functional ability in their study population could have been a reflection of the therapeutic management of early RA, as all participants received either MTX, sulfasalazine or both upon study initiation [172]. This reasoning could be applied to this pilot study, which also consisted of a very well-medicated sample population: 51.4% of

participants initiated DMARD or biologic therapy over 12 months prior to study initiation, 80% of participants were prescribed at least one DMARD at some point during the study window and 60% of participants were prescribed at least one biologic agent at some point during the study window. DMARDs and especially biologic therapy are able to suppress erosive progression and offer a possible explanation for why so little change in sum erosive damage occurred in this cohort [103], [139], [141], [144], [186], [187]. DMARDs and biologic therapy are also able to stabilize and/or improve functional ability, which is in agreement with the slight improvement in functional ability seen in this group of study participants [188]–[190]. Therefore, the tightly medicated nature of the participants in this pilot study likely minimized the changes seen in both erosive damage and functional ability, which consequently limited the range of data and potential for an association to be detected. A second potential explanation for the inability of this pilot study to detect an association between erosive damage and functional ability may relate to the stage of RA being assessed. Multiple studies suggest that functional ability is largely driven by disease activity (e.g. joint swelling and tenderness, ESR and CRP) in the early stages of RA and by joint destruction (e.g. bone erosions) in the later stages of RA [191]–[193]. Given that an early referral for RA recommendation was used at study initiation, it is possible that erosive damage may have assumed a more prominent role in changes to functional ability if a cohort of patients with well-established disease at baseline had been evaluated [180]. Overall, therapeutic and early RA implications, as well as a small sample size, were likely important contributors to the inability of this pilot

study to detect a strong, statistically significant association between change in erosive damage over time and change in functional ability.

5.2 Classification of Change in Erosive Damage over Time

In an attempt to explore how erosive damage changes over time, participants were first classified into three groups based on their total change in sum erosive damage: improvement, stable and progression. Rather than selecting an arbitrary threshold, the value of 17.1 mm³ was chosen to represent “real” change in either direction, based on smallest detectable difference measures for EERA calculated in a separate conference abstract [163]. Using this stratification scheme, 5 participants (14.3%) demonstrated improvement, 27 (77.1%) remained stable and 3 (8.6%) experienced progression. After completing the classification process, multiple tables were created to visually inspect for differences in demographic, therapeutic, diagnostic imaging, disease activity and functional ability measures among the three groups. Reported figures must be interpreted within the context of small group sizes, particularly in the improvement and progression groups, with outliers possibly skewing the values. However, it can be argued that the influence of outliers is an important part of the analysis process, as it helps to draw attention to potentially important differences among the groups. It also must be noted that this study objective focused on hypothesis-generation and did not include statistical tests; more rigorous analyses can be conducted in future studies based on the ideas developed from this pilot study. Emphasis was placed on identifying variables that may have appeared to be different among the three groups (e.g. lowest in the improvement group

and highest in progression group or vice-versa). The observations are discussed in the following subsections, with comparisons made to similar studies when possible.

Importantly, study comparisons are limited by the novel approach of EERA erosion segmentation in relation to the conventional X-ray scoring techniques used for evaluating change in erosive damage. Inter-study comparisons are further complicated by heterogeneity in study design, including RCT and natural history studies. While this pilot study is observational in nature, it involved patients within a rheumatology clinic who all received some form of treatment. Therefore, these factors should be acknowledged when comparing and contrasting findings from this study with those in the general literature.

5.2.1 Demographics

Of the five demographic variables included in this exploratory analysis (age, gender, ethnic origin, smoking status and symptom onset), only ethnic origin appeared to be notably different among the three groups. The improvement group had the smallest percentage of Caucasian participants (60%) and the progression group had the largest percentage of Caucasian participants (100%). However, 29 of the 35 study participants (82.8%) were Caucasian and any potential differences are likely a reflection of both small group sizes and lack of representation from other ethnic origins. Additionally, while the prevalence of RA has been found to vary in different ethnic groups, it is not clear whether genetic factors related to ethnicity have a role in determining the severity of the disease [2]. Collectively, possible differences in ethnic origin found among the three groups likely do not warrant further investigation.

5.2.2 Medication

Initiation of DMARD or biologic therapy 12 months prior to study initiation, as well as use of DMARDs during the study period, did not appear to be different among the three groups. However, proportions of biologic users, combination DMARD & biologic users, NSAID users and corticosteroid users were all lowest in the improvement group and highest in the progression group. At first, this finding may seem counterintuitive. The ability of DMARDs and biologics to slow disease progression and provide protection against joint damage is well-documented [139], [143], [194]–[196]. While NSAIDs are largely used for symptomatic relief, use of corticosteroids in combination with DMARDs and/or biologics has also been reported to have beneficial effects on inhibiting the progression of erosive damage [89]. Therefore, one might expect that the group displaying improvement in erosive damage would be among the most heavily medicated and that the progression group would be the most poorly medicated. However, another study assessing progression of erosive damage using X-ray over a one-year period also found a similar pattern to the one described in this study [178]. Patients in the two most aggressive therapy groups (use of DMARDs with demonstrated structural benefit, such as MTX or leflunomide, and use of biologics, such as TNF blockers) experienced the greatest progression in erosive damage. Collectively, while these findings suggest that progression of erosive disease is still possible while on DMARD and/or biologic therapy, the notion that more aggressive treatment is associated with erosive progression is likely a reflection of the rheumatologist's treatment decision-making process. Physicians are more likely to provide aggressive treatment only to patients that they identify as being the most

in need (i.e. those having the most aggressive disease), with less aggressive treatment given to those who are not expected to be at risk for progression [178], [197].

Additionally, if a patient is on biologic therapy, it is often the result of failed attempts with frontline options, such as MTX. Failure on MTX would also suggest that the patient is likely experiencing underlying erosive progression. In other words, aggressive therapy is an *effect* of disease progression.

5.2.3 Diagnostic Imaging

Baseline RAMRIS synovitis and BME scores were both considerably higher in the erosive damage improvement group, with higher scores indicating more inflammation or edema, respectively. Given the vast amount of literature supporting the ability of baseline synovitis and BME to predict subsequent radiographic progression, with inflammation and BME resulting in more damage, the findings presented here seem to be controversial. For example, Boyesen *et al.* found that baseline measures of synovitis and BME, as well as cumulative measures at the one-year time point, independently predicted radiographic progression over three years in a cohort of patients with early RA [198]. While the researchers adjusted for age, sex and ACPA levels, they did not adjust for baseline erosive damage. An analysis of baseline erosive damage in the study population of this dissertation reveals how crucial this information may be in predicting subsequent progression. RAMRIS bone erosions followed a similar pattern to synovitis and BME and were highest in the improvement group, although the stable group appeared to have slightly lower erosion scores than the progression group. In this case, EERA analysis of baseline erosive damage is a more relevant exercise, as EERA was the tool used to

originally classify patients into the three groups. Visual inspections of the baseline EERA sum erosive damage scores, which can be found in Table 4.11 of Section 4.3, suggests that the improvement group had substantially more damage at baseline than both the stable group and the progression group. In fact, the improvement group had just over five times the amount of mean baseline sum erosive damage compared to the progression group. Fautrel *et al.* found similar results when attempting to construct a matrix to predict rapid radiographic progression (RPR) in early RA patients treated with MTX or leflunomide [178]. In their proposed matrix, presence of typical RA erosions on radiographs was included as a component in the predictive model and was associated with a greater risk of RPR. Collectively, these findings emphasize that arguably the most crucial concept in attempting to determine which patients may progress and which patients may improve in terms of erosive damage is *opportunity*. A patient with no erosive disease at baseline is not able to improve; they will either remain stable or progress, as demonstrated by the low baseline damage scores seen in both of these groups. Conversely, a patient with substantial erosive damage at baseline has a much larger window for improvement to occur. Using the mean sum erosive damage for both the improvement and progression groups, a simple mathematical analysis strengthens this argument and reveals that setting an absolute threshold for classifying erosive change makes improvement easier to achieve for those with sizable damage at baseline and unlikely or impossible for those with little to no baseline damage. For an individual with baseline sum erosive damage of 233.6 mm^3 , meeting improvement classification criteria only requires a 7.3% reduction in sum damage to meet the 17.1 mm^3 threshold for EERA.

However, an individual with baseline sum erosive damage of 45.1 mm^3 would need to achieve a 37.9% reduction in sum damage to meet this threshold, and in patients with damage less than 17.1 mm^3 , improvement, as defined by this cut-off point, is not possible. Considering that 21 participants (60%) in this cohort had sum erosive damage of less than 17.1 mm^3 at baseline, it follows that 60% of participants were automatically eliminated from being considered for inclusion in the improvement group. Ultimately, these notions affirm the significance of opportunity when discussing improvement or progression in erosive damage as measured by EERA, with individuals demonstrating significant damage at baseline much more likely to experience improvement in erosive change than their low-damage counterparts.

5.2.4 Disease Activity and Functional Ability

The last two measures assessed were disease activity and functional ability. While none of the investigated factors were notably different among the three groups, baseline swollen and tender joints counts, ESR, CRP, DAS28 and HAQ-DI were all lowest in the improvement group. ESR and CRP have both been shown to be predictive of subsequent radiographic progression and swollen joint counts have also been included as a factor in predictive matrices [176], [179], [199]. While these three factors are components used in the DAS28, evidence that the total DAS28 score is associated with or can predict erosive damage is lacking. Combe *et al.* found that the DAS28 was not correlated with erosive progression [179]. Srikkum *et al.* also found that there was no correlation between erosive damage and the DAS28, although this study was cross-sectional in nature and used both semi-quantitative and quantitative measures of bone

erosions captured on high-resolution peripheral computed tomography (HR-pQCT) [134]. Like the DAS28, evidence does not support the ability of the HAQ-DI to predict erosive progression, as both Combe *et al.* and da Mota *et al.* found that baseline HAQ-DI did not predict radiographic progression [179], [199]. The lack of prominent differences among the three groups for both disease activity and functional ability outcomes, in combination with an absence of supporting evidence in the literature, suggests that both facets may not act as significant predictors of erosive change over time and are better applied in the clinical setting when treatment decisions are being considered.

5.3 Study Strengths and Limitations

The strengths of this study are rooted in the application of novel erosion segmentation software in the research setting to achieve clinically meaningful study objectives. Studies focusing on the relationship between erosive damage and functional ability have almost exclusively relied on X-ray imaging, which does not provide the same sensitivity to erosive damage as MRI. Additionally, EERA offers a fully quantitative, highly reproducible evaluation of bone erosions that allows for a more intricate examination of how erosive damage changes over time. Aside from the two study objectives, various descriptive statistics outlining the erosive characteristics of this study population (e.g. the number and location of erosions) may provide a launching point for future studies using EERA.

There are several limitations to this pilot study. Firstly, the small sample size limited the power of the study, which is the probability of correctly rejecting the null hypothesis. However, the correlation coefficients only indicated very weak associations

and future studies focusing on hypothesis-testing could verify these findings using larger sample sizes. Additionally, the nonparametric r_s did not allow for adjustment of any covariates. Baseline functional ability, older age, female gender, disease activity, RhF or ACPA positivity, radiographic damage, number of comorbidities, low education and low socioeconomic status have all been reported as predictors of poor long-term functional ability [168], [169], [200]–[207]. Once again, future studies can use the data generated from this pilot study to construct alternative statistical models that may allow for more rigorous analysis.

Secondly, only a subset of the MRx study participants drawn from the clinic of one rheumatologist was included in this pilot study. This step was necessary for logistical purposes (e.g. access to EMR, time required to schedule and conduct study visits, etc.). It is possible that this subset of study participants may not have been representative of the overall MRx study population. However, given the very detailed inclusion and exclusion criteria used at initiation of the MRx study, it is unlikely that any significant differences existed. Additionally, all rheumatologists participating in the MRx study were located in Hamilton, Ontario, Canada, which reduces the variability associated with heterogeneous RA cohorts from different geographical populations.

Thirdly, only one hand was imaged for this study. While imaging and analyzing both hands for erosive damage would have provided a more comprehensive approach, participant comfort was made a priority given the debilitating and often painful nature of RA; performing two scans back-to-back was not deemed appropriate in terms of both patient burden and scheduling. However, in a conference abstract, Tomizza *et al.* reported

that performing an MRI of only the MCPs of the dominant hand still resulted in 1.3 times the number of patients identified with erosive disease compared to X-ray [129]. Although this abstract focused on the dominant hand and used RAMRIS for MRI analysis rather than EERA, the highly sensitive nature of MRI to bone erosions helps to offset concerns about evaluating only one hand.

Fourthly, the medication documentation process for this study was based on prescription logs and did not take adherence into account. Adherence for DMARDs and biologics is quite variable, with adherence to biologic therapies reported as low as 11% [208], [209]. Based on the long-standing nature of the relationship between many of the patients in this sample population and the practicing rheumatologist, adherence issues, though possible, are less likely. Additionally, medication data collection did not take into account dose, different drugs within the same class (e.g. etanercept vs. adalimumab or MTX alone vs. MTX in combination with leflunomide) or duration of treatment. Collectively, these limitations would be more significant if this study were a RCT aiming to evaluate the impact of differences in treatment strategies on the progression of erosive damage. This study was observational and the investigation of medication effects on erosive disease was not a primary study objective. Medication data were only collected as an outcome to be used for descriptive statistics and to explore potential connections with change in sum erosive damage that may warrant further investigation under a more rigorous framework, such as an RCT.

Lastly, due to the fact that two separate investigators conducted the baseline and follow-up study visits, potential sources of bias emerge in two specific areas. Joint counts

were not performed by the same assessors at baseline and follow-up study visits and reported inter-rater reliability is variable, especially for swollen joint counts [210]. Therefore, comparisons made between joint counts and DAS28 scores at baseline and follow-up should be made carefully, although both measures served a primarily descriptive role and neither was used in statistical analysis. Two raters were also involved in EERA analysis (MJ at baseline and MT at follow-up), which may have introduced variability in the segmentation of erosions. However, the inter-rater single measures and average measures ICCs (95% CI) for these two readers were 0.867 (0.686 to 0.947) and 0.928 (0.814 to 0.973), respectively, which indicates exceptional agreement.

5.4 Conclusions and Future Directions

In this longitudinal pilot study using EERA software for quantifying bone erosive damage in the MCP 2-5 joints of the worst-affected hand in patients with RA, the null hypothesis that total change in sum erosive damage and rate of change in sum erosive damage are not associated with change in functional ability could not be rejected. In terms of exploring how sum erosive damage changes over time, participants were classified into three groups: improvement, stable and progression. Of the numerous demographic, therapeutic, diagnostic imaging, disease activity and functional ability outcomes examined among the three groups using a visual, non-statistical approach, baseline erosive damage emerged as the most notable factor. Individuals in the erosive improvement group appeared to have more than five times the baseline mean sum erosive damage compared to the progression group, illustrating the construct that improvement is only possible when sufficient damage exists in the first place. Additionally, the

progression group appeared to be the most heavily medicated, which is likely a reflection of the physician's ability to recognize the patients who are in the greatest need of aggressive treatment. The information and various interpretations provided in this pilot study warrant further investigation using more advanced statistical tests. Ultimately, EERA is an exciting tool for quantification of bone erosions in patients with RA and studies in both the research and clinical setting should continue to explore the applications of this software in ways that enhance our understanding of the disease process and patient outcomes.

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Appendix A: Informed Consent Form

Local Principal Investigator:

Dr. Jonathan D. Adachi, MD,
FRCPC

Principal Investigator:

Mr. Michael Tomizza, BSc, MSc
Candidate

There are no external sponsors for this study.

You are invited to participate in the research study described in this form. After reading this, you can ask questions and decide to participate. The decision to participate is completely up to you. If you decide not to participate, you will still receive the same quality of care from your doctor.

Study Description

In this study, we will assess changes in erosion volume over time in patients with rheumatoid arthritis (RA) using magnetic resonance imaging (MRI) and software entitled Early Erosions in Rheumatoid Arthritis (EERA). This study is an extension of work done by a former PhD student of Dr. Adachi's, Ruben Tavares, and as a previous participant in Mr. Tavares' study, we are inviting you to participate in this follow-up study. 30-40 participants from Mr. Tavares' study will be followed up with another MRI of the hand most severely affected. Changes in erosion size will be quantified to see if there is a relationship between erosion progression and quality of life. The relationship between joint counts and erosions will also be investigated.

Background

Rheumatoid arthritis can be a severely debilitating disease. MRI has emerged as an important research tool for studying RA, due to its ability to detect erosions earlier than conventional X-rays. Physicians use MRI to assess RA patients; however, one of the barriers to using MRI in the clinical setting is the lack of a simple, time-efficient, and highly reproducible technique for analysis of images. EERA represents a possible solution to this problem. It provides a fully quantitative value of MRI erosion size that is faster and less subjective than current MRI analysis measures. EERA has been shown to have high agreement between users, but studies have not assessed its ability to monitor progression of erosion size over time. The ability of EERA to potentially measure erosion progression could improve the way that physicians track erosions, which is an important method in assessing drug effectiveness and classifying stages of the disease process.

Your Responsibilities

This study is designed to revolve around standard of care, reducing the burden to the participant. The measures being investigated would be conducted as part of your physician's routine assessment of RA, regardless of the study. As a previous participant of Ruben Tavares and Dr. Adachi, the methods of this study will be familiar to you. You will be asked to complete the following tasks:

1. MRI

As noted, MRI is part of standard of care in RA. You will have an MRI done on your hand most severely affected by RA. The scan itself should take 25-30 minutes, and the whole process (including joint counts, questionnaires, etc; see #2 and #3 below) should take approximately 2 hours. If possible, we will attempt to schedule the MRI on the same day as your normally scheduled appointment with Dr. Adachi. However, due to scheduling reasons, a separate, one-time study visit for the MRI and other study measures is likely and will be arranged for a date and time that is convenient for you, as close to your original appointment as possible.

2. HUI3 and HAQ

The Health Utilities Index Mark 3 (HUI3) and Health Assessment Questionnaire (HAQ) are questionnaires designed to assess quality of life. You would have completed the HUI3 and the HAQ for the previous study. You will be asked to complete them at the time of your scheduled MRI visit.

3. DAS28

The Disease Activity Score 28 (DAS28) is a comprehensive measure of disease activity used in standard arthritis care that consists of a tender joint count, swollen joint count, blood measurements (erythrocyte sedimentation rate, ESR, and C-reactive protein, CRP) and a patient global health assessment, where you are asked to rank your overall health on a scale of 0-100. The joint counts and health assessment will be administered at the time of your MRI visit, and the blood work will be requested at your normally scheduled appointment with Dr. Adachi.

Foreseeable Risks and Costs to Participation

MRI is a safe procedure, as it does not expose patients to radiation. It is possible that pain or discomfort during the MRI scan may occur in some patients with more severe RA

due to the sitting required. However, scanning only the most affected hand will reduce scan time and the scan can be stopped at any time.

You will be reimbursed for parking, should the MRI visit be scheduled on a day separate from your normally scheduled appointment with Dr. Adachi.

Potential Benefits

There are three possible ways in which potential benefits may be seen from this study. Firstly, participants may experience benefits, as they will receive information regarding the actual size of their erosions and how they have progressed over time. This information is not normally available to the RA population.

Secondly, doctors may benefit from the results of this study. If this study, as well as further research, demonstrates that EERA can be used to successfully track erosion progression and connections exist to clinical measures, physicians may have at their disposal a quick and reliable tool for evaluating erosions and providing the best care possible.

Lastly, society may ultimately benefit from this study. The true beneficiary of a system that allows for more efficient monitoring of disease progression is the entire RA community.

Early Termination of Study Participation

If you wish to withdraw from the study at any point, including during the MRI scan, you will be allowed to do so without penalty and without any impact on the quality of care received from your physician. You will be asked, but not required, to provide a reason for withdrawal, as this information may prove to be important for data analysis. You will be asked if any data collected prior to withdrawal may be used. If you wish not to have your data included in the study, it will be destroyed. Your informed consent form, along with a document outlining your decision to withdraw, will be filed to ensure that proper withdrawal procedures have been followed.

Confidentiality

Study staff are required by law to keep your information private. Personal information, such as your name, address and telephone number, will be used for the sole purposes of scheduling and sharing study results. Your study results will be shared with

Dr. Adachi and will not be shared with fellow participants. You may be asked to update this information if it has changed since initial collection. Information relating to medical history, such as age, sex, drug therapy, and clinical scores, will be linked to your contact information through a unique identification number.

All participant information will be stored in a locked office, either in a locked filing cabinet or electronically on computers with password protection. Viewing privileges will be restricted to the Master's student, Dr. Adachi, and members of Dr. Adachi's clinic if information needs to be verified (ie. change in information, etc.). The information collected will be kept for potential future studies investigating various aspects of rheumatoid arthritis, with the same protection of privacy upheld. All files will be destroyed 10 years after the completion of the study.

The Research Ethics Board and health authorities have the ability to view your medical records in order to verify information collected during the study. However, they are required by law to keep this information confidential.

Disclosure of Study Information

Study results will be presented to you in the form of a follow-up call or at your regularly scheduled appointment with Dr. Adachi. Study results will be presented to the scientific community in the form of abstracts, conferences, reports, and scientific journals. Your personal information will never be included in these study summaries.

Contact Information

If you have any questions or comments about the study, you may contact Dr. Adachi at 25 Charlton Avenue East, Suite 501, Hamilton, ON L8N 1Y2 T:905-529-1317.

If you have any questions regarding your rights as a research participant, you may contact the Coordinator of the Hamilton Integrated Research Ethics Board (HiREB) at 905-521-2100 ext. 42013.

Consent Disclosure

Circle one

I confirm that I have read and fully understand this informed consent form. YES NO

All technical language and answers to my questions have been explained to my satisfaction. YES NO

The consent was explained to me and I have had the opportunity to ask questions. YES NO

I agree to participate in this study. YES NO

I will receive a signed copy of this form. YES NO

Name of Participant Signature of Participant Date

Consent form administered and explained in person by

Name of Person Obtaining Informed Consent Signature of Person Obtaining Informed Consent Date

Name of Principal Investigator Signature of Principal Investigator Date

Appendix B: Data Collection Form

STUDY ID: _____ **STUDY VISIT DATE:** _____ / _____ / _____
YEAR MONTH DAY

1.0 EROSION VOLUMES

To be completed after study visit.

1.1 *Sum of Erosions at Baseline:* _____ mm³ *Date:* _____ / _____ / _____

1.2 *Sum of Erosions at Present:* _____ mm³ *Date:* _____ / _____ / _____

1.3 *Net Change in Erosions:* _____ mm³ *Time Span:* _____ months

1.4 *Rate of Change:* _____ mm³/month x 12 = _____ mm³/yr

2.0 HEALTH UTILITIES INDEX MARK 3 (HUI3) SCORES

2.1 *HUI-3 at Baseline:* _____

2.2 *HUI-3 at Present:* _____

3.0 HEALTH ASSESSMENT QUESTIONNAIRE (HAQ) SCORES

3.1 *HAQ at Baseline:* _____

3.2 *HAQ at Present:* _____

4.0 DISEASE ACTIVITY SCORES (DAS28)

4.1 Baseline

- *Swollen Joint Count:* _____
- *Tender Joint Count:* _____
- *ESR:* _____ mm/hr
- *CRP:* _____ mg/L
- *Patient Global Health:* _____
- = *DAS28:* _____

4.2 Present

- *Swollen Joint Count:* _____
- *Tender Joint Count:* _____
- *ESR:* _____ mm/hr
- *CRP:* _____ mg/L
- *Patient Global Health:* _____
- = *DAS28:* _____

5.0 OTHER CLINICAL MEASURES FROM EMR

6.0 MEDICATIONS

<u>Drug</u>	<u>Dose</u>	<u>Duration/Commencement</u>	<u>Other</u>
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Appendix C: Joint Count Protocol

** Note: This protocol was prepared and written during the MRx study and was used to guide joint counts performed at follow-up. Minor edits to wording and overall structure have been made by MT.*

This document outlines training for properly executing joint assessments on MRx study participants. The method outlined here is one of several examination methods to determine the 28-joint swollen and tender joint count (SJC and TJC, respectively) assessment of joint deformities and extra-articular features. This document also provides an overview of which joints are applicable. On study forms, the homunculus is positioned anteriorly (same orientation as if you were facing a patient), hence the right side information is recorded on the left side of the homunculus and the left side is recorded on the right of the homunculus.

Neither bony swelling, deformity or edema surrounding the joints constitute joint swelling. Decreased range of motion may indicate swelling.

Swelling is an increase in fluids in the tissue that surrounds the joint and in the joint capsule. This swelling may cause tenderness, stiffness or decreased range of motion.

HAND

Inspect patients' wrist and hands prior to palpation, to avoid compromising the area. If possible, have patient place hands on thighs or on a pillow provided to them to avoid their hands being suspended in mid-air.

Observe any redness, swelling, alignment changes, muscle wasting at aspects of hands (palm and back), nodules at meta-carpal phalangeal (MCPs) and PIPs.

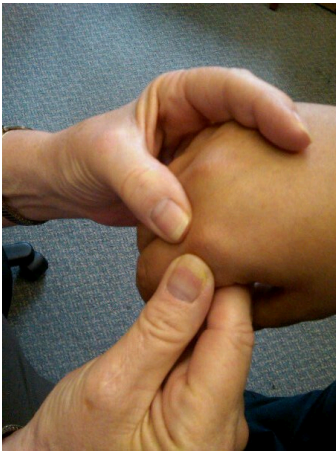
Ask patient to supinate (turn) palm upward to inspect palms for above findings.

Palpation: Use enough pressure to blanch your fingertips, without causing undue discomfort to the patient. If too much pressure is applied, it will force fluid out of the capsule and be difficult or impossible to detect. If joints look very swollen or sore, it would be safe to note changes, without palpation. Note findings with an "X" on the homunculus in appropriate area.

To palpate the MCPs, support the patient's hand in yours, with their fingers slightly flexed (see photograph on next page). Find the joint line on the palm of the hand by

having the patient move their finger, as well as checking for crepitus. Place your thumbs on either side of joint line on anterior aspect at 4 and 8 o'clock. Holding one thumb against joint line, lift and press with the other thumb to move any possible fluid against the stable thumb. If unsure if moving fluid or soft tissue, try pressing with one thumb only, then two again. If it feels the same with one thumb as two, it is likely soft tissue. Note any bony changes or synovial thickening.

If any MCP indicates subluxation (uneven alignment-partial dislocation), gently realign before palpating (place light pressure on palm surface with finger to raise phalange into normal position). Palpate as above. The joint line may be diminished if there is sufficient fluid in joint.



Palpate the PIP and distal interphalangeal (DIP) joints: gently palpate these joints to illicit tenderness and/or swelling. Using the four-finger method to ballot fluid (see photograph below), place your thumb and forefinger of one hand on either side of joint line. Place your other thumb and forefinger above and below joint line. Apply pressure with the remaining finger while holding 2 or 3 fingers gently in place on joint line. This will move any potential fluid through the joint against the stable finger.



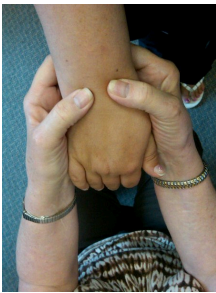
The joints can be tender without swelling, and vice versa.

Reddened, boggy looking areas are likely acute (new, painful). Firm, thickened areas are likely chronic (ongoing synovial activity, not generally painful unless patient is experiencing a flare). Inquire if this is common to the patient or a new occurrence.

If joints feel hardened or thickened, or the joint line is diminished, it may be a result of synovial thickening, alignment changes, subluxation, joint narrowing or bony changes (van Riel et al. 2004).

WRIST

Observe swelling and/or alignment changes that may be present. Supporting the patient's hand, gently palpate over the ulnar styloid, across joint line and over radial styloid (styloid-bony prominence on either side of wrist; radial – thumb side; ulnar – opposite side) and across each row of carpals (see photograph below). These are the small bones, proximal to the wrist (toward fingers) and are approximately 2 finger widths across back of hand. Next, with fingers of other hand under joint line and thumb over joint line, passively flex and extend patients hand at wrist to determine crepitus or tenderness at the wrist joint. (Passive-you are performing the movement for the patient).



ELBOW

Observe possible swelling, any alignment changes at the olecranon bursa (head of the ulna) while patient's arm is at approximately 90 degrees.

Palpate the epicondyles (dimples at sides of elbow) and olecranon bursa (back of elbow) for swelling and tenderness. (see photograph on next page).

Holding patient's forearm, gently flex their arm at elbow toward shoulder, and then extend arm to about 180 degrees (straight out at shoulder height) to illicit potential tenderness, crepitus or alignment changes at elbow.



SHOULDER

Observe any swelling or alignment changes. Swelling may be difficult to see, if at all, since the shoulder is a deep joint. It may be seen on top of the shoulder or in the bicipital groove. The bicipital groove borders on the glenohumeral joint at the front of the shoulder. The Deltoid bursa is located at the top of the arm up and over the shoulder. The Acromioclavicular joint (AC) is at the end of the clavicle (collar bone). Palpate these areas with a fluid motion. Place a thumb on the AC joint and wrap your fingers around the shoulder (see photograph on next page). Palpate the bursa and joint line with your fingertips and the AC joint with your thumb; slide your thumb from the AC joint to the bicipital groove and palpate for tenderness and swelling (adapted from van Riel et al. 2004). The AC joint can be the cause of significant pain, loss of range of motion and impingement.

Holding the patient's forearm and upper arm, raise his/her arm forward and straight up overhead, observing limitations or expression of pain. Feel for crepitus as the patients' arm is gently lowered.

Once you have noted swelling and pain, there is no need to further palpate or move the articulations of the joint in question. Simply gently move the patient's arm back to rest position.

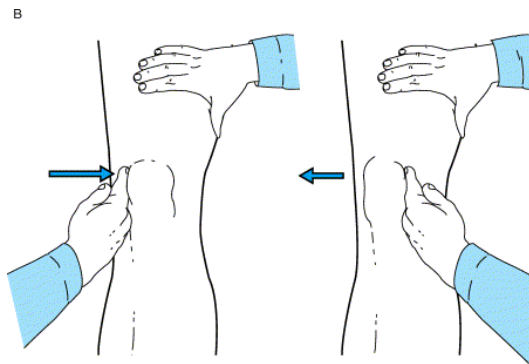


KNEE

Ask patient to bring foot slightly forward on the floor, to about 45 degrees at knee.

Locate joint line (approx. 2 finger widths below patella and slightly above the tibia). Palpate the joint line with thumbs, about 5cm. apart, to allow potential fluid to move between digits. The joint line of the knee is similar to a smile (see photograph below; van Riel, 2004).

Palpate for swelling, tenderness and alignment changes. Swelling is not necessarily detectable at the joint line, but tenderness may be present. Swelling could be difficult to access through clothing.



OVERALL TIPS

- Watch for the patient's facial expression while palpating. The patient may not admit to tenderness, but wincing or abruptly looking away could signal possible soreness. Inform the patient that any slight/mild discomfort or "awareness" of the uncomfortable sensation of their joints during the joint count is also categorized as tenderness.
- Using words like "tender" and "sensitive" can be easier to comprehend than "pain" and "hurt."
- Be mindful of that many patient's have very sensitive joints; a gentle touch can elicit the necessary findings without causing undue pain for the patient.

CONCLUSION AND REFERENCE

The aforementioned descriptions summarize the joint assessment procedure to be used in the MRx study and are consistent with the method endorsed by the developer of the Disease Activity Score (van Riel et al. 2004):

van Riel P, Fransen J, Scott DL. Eular Handbook of Clinical Assessments Rheumatoid Arthritis. Nijmegen, 2004.

Appendix D: Swollen Joint Count Homunculus

OPERA		BASELINE: CLINICAL EXAMINATION (PAGE 9 OF 10)		CRF 303	
OPERA110		CRF #303		VISIT #001	
SUBJECT ID: 		SUBJECT INITIALS: 		INVESTIGATOR NO: 	
<small>Centre ID Subject ID</small>		<small>F L</small>			
SWOLLEN JOINT COUNT OFFICE USE ONLY					
Please indicate which of the patient's joints have SWELLING today by filling in (●) each affected joint in the homunculus below.					
Completed? <input type="checkbox"/> Yes <input type="checkbox"/> No					
Completed by: _____ <div style="text-align: center;">Print Name</div>					
Signature: _____					
IF AT LEAST 3 AREAS ARE SWOLLEN, (at least 3 of the following 14 areas bilaterally: PIP, MCP, wrist, elbow, knee, ankle, and MTP joints)					
How long has this swelling endured? _____ days OR _____ weeks <input type="checkbox"/> Not Applicable (less than 3 areas affected)					
IF there is SWELLING OF EITHER THE WRIST(s), MCP(s) or PIP(s), how long has this swelling endured? _____ days OR _____ weeks <input type="checkbox"/> Not Applicable (wrists, MCPs, or PIPs not affected)					
IF there is simultaneous involvement on both sides of the body of either the PIPs, MCPs, or MTPs, how long has this symmetrical swelling endured? _____ days OR _____ weeks <input type="checkbox"/> Not Applicable (No symmetry / PIP, MCP or MTPs not involved)					

Appendix E: Tender Joint Count Homunculus

OPERA BASELINE: CLINICAL EXAMINATION (PAGE 8 OF 10) CRF 008

OPERA #110 CRF #008 VISIT #001
 SUBJECT ID: SUBJECT INITIALS: INVESTIGATOR NO:
Centre ID Subject ID F L

OFFICE USE ONLY

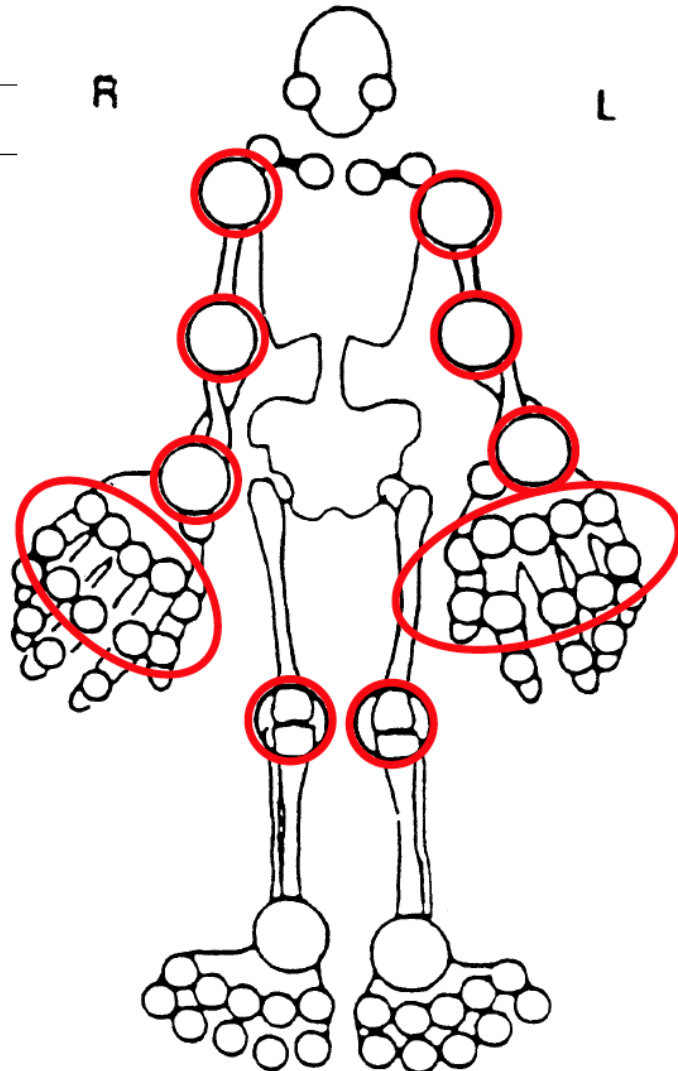
TENDER JOINT COUNT

Please indicate which of the patient's joints have TENDERNESS today by marking each affected joint with a cross (⊗) in the homunculus below.

Completed? ☐ Yes ☐ No

Completed by: _____
Print Name

Signature: _____



Appendix F: Magnetic Resonance Imaging Safety Form

REQUEST FOR ORTHONE MRI SCAN

<p style="text-align: center;">CAMRIS</p> <p>612-25 Charlton Ave. E. Hamilton, ON L8N 1Y2 Phone: 905.527.0028</p> <p>Exam Requested: <u>MRx XX PE HYBRID (Ruben)</u></p> <p>Study Visit:</p> <table style="width: 100%;"> <tr> <td><input type="checkbox"/> Baseline</td> <td><input type="checkbox"/> 18 Month</td> </tr> <tr> <td><input type="checkbox"/> 6 Month</td> <td><input type="checkbox"/> 24 Month</td> </tr> <tr> <td><input type="checkbox"/> 12 Month</td> <td></td> </tr> </table> <p>Worst Affected Hand at Baseline</p> <p><input type="checkbox"/> Left <input type="checkbox"/> Right <input type="checkbox"/> Equal</p> <p>Dominant Hand:</p> <p><input type="checkbox"/> Left <input type="checkbox"/> Right</p>	<input type="checkbox"/> Baseline	<input type="checkbox"/> 18 Month	<input type="checkbox"/> 6 Month	<input type="checkbox"/> 24 Month	<input type="checkbox"/> 12 Month		<p>MRx ID: _____</p> <p>Last Name: _____</p> <p>First Name: _____</p> <p>Address: _____</p> <p>City: _____ Prov.: _____</p> <p>Postal Code: _____</p> <p>Phone: (W) _____ (H) _____</p> <p>Weight: _____ Height: _____</p> <p>Appointment (Date) _____ (Time) _____</p>
<input type="checkbox"/> Baseline	<input type="checkbox"/> 18 Month						
<input type="checkbox"/> 6 Month	<input type="checkbox"/> 24 Month						
<input type="checkbox"/> 12 Month							

<p>Is there any possibility that you may be pregnant?</p> <p>Have you ever worked with metal (hobby/occupation)?</p> <p>Please check if you have any of the following:</p> <table style="width: 100%;"> <tr><td>Pacemaker, defibrillator, pace wires</td><td><input type="checkbox"/> Yes</td><td><input type="checkbox"/> No</td></tr> <tr><td>Prosthetic heart valve</td><td><input type="checkbox"/> Yes</td><td><input type="checkbox"/> No</td></tr> <tr><td>Electrodes, shunts, plates, aneurysm clips</td><td><input type="checkbox"/> Yes</td><td><input type="checkbox"/> No</td></tr> <tr><td>Vascular access port or catheter</td><td><input type="checkbox"/> Yes</td><td><input type="checkbox"/> No</td></tr> <tr><td>Intravascular coils, filters or stents</td><td><input type="checkbox"/> Yes</td><td><input type="checkbox"/> No</td></tr> <tr><td>Insulin pump or infusion pump</td><td><input type="checkbox"/> Yes</td><td><input type="checkbox"/> No</td></tr> <tr><td>Cochlear, stapes or orbit/ear implants</td><td><input type="checkbox"/> Yes</td><td><input type="checkbox"/> No</td></tr> <tr><td>Bone growth/fusion stimulator</td><td><input type="checkbox"/> Yes</td><td><input type="checkbox"/> No</td></tr> <tr><td>Implanted <u>neurostimulator</u></td><td><input type="checkbox"/> Yes</td><td><input type="checkbox"/> No</td></tr> <tr><td>Metal or wire mesh implants</td><td><input type="checkbox"/> Yes</td><td><input type="checkbox"/> No</td></tr> <tr><td>Artificial limb or joint</td><td><input type="checkbox"/> Yes</td><td><input type="checkbox"/> No</td></tr> <tr><td>Metal rods, pins or plates in a joint or bone</td><td><input type="checkbox"/> Yes</td><td><input type="checkbox"/> No</td></tr> <tr><td>Bullets or shrapnel in your body</td><td><input type="checkbox"/> Yes</td><td><input type="checkbox"/> No</td></tr> <tr><td>Metal fragments in your eye(s)</td><td><input type="checkbox"/> Yes</td><td><input type="checkbox"/> No</td></tr> <tr><td>Tattoos, tattooed makeup, body piercing</td><td><input type="checkbox"/> Yes</td><td><input type="checkbox"/> No</td></tr> <tr><td>Any other implanted device</td><td><input type="checkbox"/> Yes</td><td><input type="checkbox"/> No</td></tr> </table> <p>Please check if you have ever had any of the following:</p> <table style="width: 100%;"> <tr><td>Brain, ear, eye or head surgery</td><td><input type="checkbox"/> Yes</td><td><input type="checkbox"/> No</td></tr> <tr><td>Vascular (vein) surgery</td><td><input type="checkbox"/> Yes</td><td><input type="checkbox"/> No</td></tr> <tr><td>Bone or joint surgery</td><td><input type="checkbox"/> Yes</td><td><input type="checkbox"/> No</td></tr> </table> <p>Before your MRI, please REMOVE shoes and ALL metal objects, including:</p> <table style="width: 100%;"> <tr> <td><u>hearing aid</u></td> <td>barrettes/hair pins</td> <td>safety pins/clips</td> <td>jewelry/keys</td> </tr> <tr> <td><u>credit cards</u></td> <td>pocket knife</td> <td>coins/change</td> <td>pens/pencils</td> </tr> <tr> <td><u>watch</u></td> <td>cellular phone/pager</td> <td>clothing/undergarments containing metal</td> <td></td> </tr> </table>	Pacemaker, defibrillator, pace wires	<input type="checkbox"/> Yes	<input type="checkbox"/> No	Prosthetic heart valve	<input type="checkbox"/> Yes	<input type="checkbox"/> No	Electrodes, shunts, plates, aneurysm clips	<input type="checkbox"/> Yes	<input type="checkbox"/> No	Vascular access port or catheter	<input type="checkbox"/> Yes	<input type="checkbox"/> No	Intravascular coils, filters or stents	<input type="checkbox"/> Yes	<input type="checkbox"/> No	Insulin pump or infusion pump	<input type="checkbox"/> Yes	<input type="checkbox"/> No	Cochlear, stapes or orbit/ear implants	<input type="checkbox"/> Yes	<input type="checkbox"/> No	Bone growth/fusion stimulator	<input type="checkbox"/> Yes	<input type="checkbox"/> No	Implanted <u>neurostimulator</u>	<input type="checkbox"/> Yes	<input type="checkbox"/> No	Metal or wire mesh implants	<input type="checkbox"/> Yes	<input type="checkbox"/> No	Artificial limb or joint	<input type="checkbox"/> Yes	<input type="checkbox"/> No	Metal rods, pins or plates in a joint or bone	<input type="checkbox"/> Yes	<input type="checkbox"/> No	Bullets or shrapnel in your body	<input type="checkbox"/> Yes	<input type="checkbox"/> No	Metal fragments in your eye(s)	<input type="checkbox"/> Yes	<input type="checkbox"/> No	Tattoos, tattooed makeup, body piercing	<input type="checkbox"/> Yes	<input type="checkbox"/> No	Any other implanted device	<input type="checkbox"/> Yes	<input type="checkbox"/> No	Brain, ear, eye or head surgery	<input type="checkbox"/> Yes	<input type="checkbox"/> No	Vascular (vein) surgery	<input type="checkbox"/> Yes	<input type="checkbox"/> No	Bone or joint surgery	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<u>hearing aid</u>	barrettes/hair pins	safety pins/clips	jewelry/keys	<u>credit cards</u>	pocket knife	coins/change	pens/pencils	<u>watch</u>	cellular phone/pager	clothing/undergarments containing metal		<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
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<u>watch</u>	cellular phone/pager	clothing/undergarments containing metal																																																																				

Referring Physician: _____	Date: _____
Patient Signature: _____	Date: _____

Appendix G: Health Assessment Questionnaire- Disability Index

HEALTH ASSESSMENT QUESTIONNAIRE (HAQ-DI)©

Name: _____

Date: _____

Please place an "x" in the box which best describes your abilities **OVER THE PAST WEEK**:

	WITHOUT ANY DIFFICULTY	WITH SOME DIFFICULTY	WITH MUCH DIFFICULTY	UNABLE TO DO
<u>DRESSING & GROOMING</u>				
Are you able to:				
Dress yourself, including shoelaces and buttons?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Shampoo your hair?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<u>ARISING</u>				
Are you able to:				
Stand up from a straight chair?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Get in and out of bed?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<u>EATING</u>				
Are you able to:				
Cut your own meat?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Lift a full cup or glass to your mouth?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Open a new milk carton?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<u>WALKING</u>				
Are you able to:				
Walk outdoors on flat ground?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Climb up five steps?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Please check any **AIDS OR DEVICES** that you usually use for any of the above activities:

<input type="checkbox"/> Devices used for Dressing (button hook, zipper pull, etc.)	<input type="checkbox"/> Built up or special utensils	<input type="checkbox"/> Crutches
<input type="checkbox"/> Special or built up chair	<input type="checkbox"/> Cane	<input type="checkbox"/> Wheelchair
	<input type="checkbox"/> Walker	

Please check any categories for which you usually need **HELP FROM ANOTHER PERSON**:

<input type="checkbox"/> Dressing and grooming	<input type="checkbox"/> Arising	<input type="checkbox"/> Eating	<input type="checkbox"/> Walking
--	----------------------------------	---------------------------------	----------------------------------

Please place an "x" in the box which best describes your abilities **OVER THE PAST WEEK**:

	WITHOUT ANY DIFFICULTY	WITH SOME DIFFICULTY	WITH MUCH DIFFICULTY	UNABLE TO DO
<u>HYGIENE</u>				
Are you able to:				
Wash and dry your body?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Take a tub bath?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Get on and off the toilet?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<u>REACH</u>				
Are you able to:				
Reach and get down a 5 pound object (such as a bag of sugar) from above your head?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Bend down to pick up clothing from the floor?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<u>GRIP</u>				
Are you able to:				
Open car doors?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Open previously opened jars?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Turn faucets on and off?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<u>ACTIVITIES</u>				
Are you able to:				
Run errands and shop?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Get in and out of a car?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Do chores such as vacuuming or yard work?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Please check any **AIDS OR DEVICES** that you usually use for any of the above activities:

<input type="checkbox"/> Raised toilet seat	<input type="checkbox"/> Bathtub bar	<input type="checkbox"/> Long-handled appliances for reach
<input type="checkbox"/> Bathtub seat	<input type="checkbox"/> Long-handled appliances in bathroom	<input type="checkbox"/> Jar opener (for jars previously opened)

Please check any categories for which you usually need **HELP FROM ANOTHER PERSON**:

<input type="checkbox"/> Hygiene	<input type="checkbox"/> Reach	<input type="checkbox"/> Gripping and opening things	<input type="checkbox"/> Errands and chores
----------------------------------	--------------------------------	--	---

Appendix H: Rheumatoid Arthritis Magnetic Resonance Imaging Scoring Form

OPERA		BASELINE: MRI ASSESSEMENT (PAGE 1 OF 2)										CRF 021	
OPERA #110		CRF #021					VISIT #001						
SUBJECT ID: <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>		SUBJECT INITIALS: <input type="text"/> <input type="text"/>		INVESTIGATOR NO: <input type="text"/> <input type="text"/>		DATE OF VISIT: <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>							
<small>Centre ID Subject ID</small>		<small>F L</small>				<small>year</small>		<small>month (e.g. JAN)</small>		<small>day</small>			
Study Subject ID: <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>				↑ OFFICE USE ONLY ↑									

The guidelines below will be used conjunction with the OMERACT image atlas (Conaghan P, *et al.* Ann Rheum Dis 2005;64(Suppl 1):i11-21) to score the MRIs of the MCP joints for the study.

SCORING OF SYNOVITIS

SYNOVITIS is scored on a scale from 0 to 3. 0 is normal, while the scores of 1 to 3 increase by thirds of the presumed maximum volume of enhanced tissue in the synovial compartment on T2-weighted images compared to normal synovial volume:

0) Normal: 0% 1) Mild: 1-33% 2) Moderate: 34-66% 3) Severe: 67-100%

	MCP Joint				Subtotal Score
	2	3	4	5	
Synovitis (0-3)	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>

SCORING OF BONE EROSION AND BONE OEDEMA

Score the following from the articular surface (or its best estimated position if absent) to a depth of 1 cm.

BONE EROSION is scored 0-10, according to the proportion (in increments of 10%) of bone involved:

0) 0% 1) 1-10% 2) 11-20% 3) 21-30% 4) 31-40%
 5) 41-50% 6) 51-60% 7) 61-70% 8) 71-80% 9) 81-90% 10) 91-100%

		MCP Joint				Subtotal Score
		2	3	4	5	
Bone erosion (0-10)	Proximal	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
	Distal	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>

BONE OEDEMA is scored 0-3, according to the proportion (in increments of 33%) of bone involved:

0) 0% 1) 1-33% 2) 34-66% 3) 67-100%

		MCP Joint				Subtotal Score	Total Score
		2	3	4	5		
Bone oedema (0-3)	Proximal	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
	Distal	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	

Scored by: _____
 Print Name

Date:
year month (e.g. JAN) day

Signature: _____

OPERA_bline_DCR_MRI_01FEB2011

Baseline: MRI Assessment Page 1 of 2

Date: yyyy / MMM / dd
 PI/CoI/SC Initials: _____